The American Journal of Medicine

1951

The American Journal of Medicine

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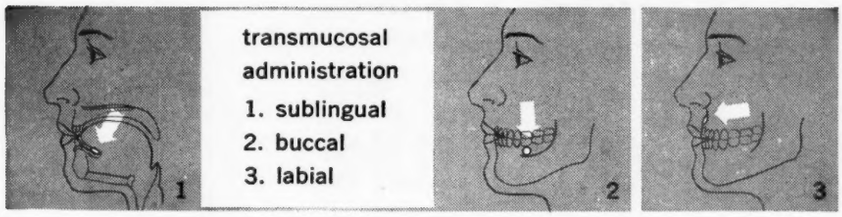
new trend in hormone therapy



"parenteral therapy without injection"

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TESTOSTERONE (Funk) 3 mg., 5 mg.
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Orasorbs are specially prepared tablets of the free crystalline hormones (Funk) for transmucosal absorption directly into the systemic circulation..."parenteral therapy without injection."

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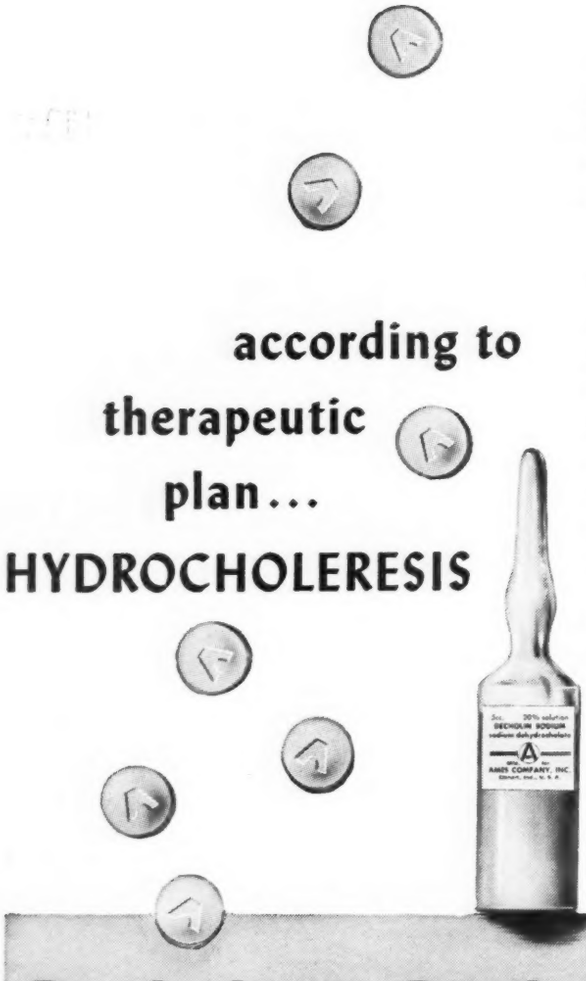

according to therapeutic plan... HYDROCHOLERESIS

In biliary tract disorders, present-day medical management hinges on stimulation therapy and non-surgical drainage. A therapeutic plan is to flush and drain the hepatobiliary tract by *increasing the volume of bile while reducing its viscosity,* solid content and specific gravity.

This dual action—*hydrocholeresis*—is evoked in full accord with the therapeutic plan by the administration of *Decholin* and its sodium salt (*Decholin Sodium*), the most potent hydrocholeretic agents available. A less pronounced effect attends the use of *choleretics,* such as combinations of bile salts, which produce but slight increase in bile of high viscosity—a procedure which may defeat this therapeutic plan.

When the therapeutic plan specifies *hydrocholeresis, Decholin* and *Decholin Sodium* are the indicated agents—they are specifically hydrocholeretic. Begin therapy with small doses and progressively increase the dosage of *Decholin Sodium* (intravenously). This is then followed by a course of *Decholin* Tablets.

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Tablets of 3¾ gr.
in bottles of 25, 100, 500, 1000 and 5000.

brand of sodium dehydrocholate

In 20% aqueous solution:
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boxes of 3, 20 and 100.

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Ames Company of Canada, Ltd., Toronto

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"...the only drug we have seen that allays anxiety without clouding consciousness"

J.A.M.A. *140*:672 (June 25) 1949.

Tolserol *(Squibb Mephenesin)*

- **to alleviate pronounced anxiety and tension**
- **as an adjunct in the treatment of chronic alcoholics**

DOSAGE

In anxiety tension states:

As little as 0.5 Gm., given orally every few hours, has produced a good response. However, for optimum effect, 0.75 Gm. or more is given several times a day.

As an adjunct in the treatment of chronic alcoholics:

As much as 3 Gm. orally every four hours has been found useful in the acute stage. This dosage is reduced when the patient becomes more manageable. (If Tolserol is given too soon after the patient drank alcohol, the toxic effect of the alcohol may be potentiated. For this reason, Tolserol should not be administered until six hours have elapsed since the patient drank alcohol.)

Tablets, 0.5 Gm., 0.25 Gm.; *Capsules*, 0.25 Gm.; *Elixir*, 0.1 Gm. per cc.; *Solution*, 2% (intravenous).

Tolserol *(Squibb Mephenesin)*

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The American Journal of Medicine

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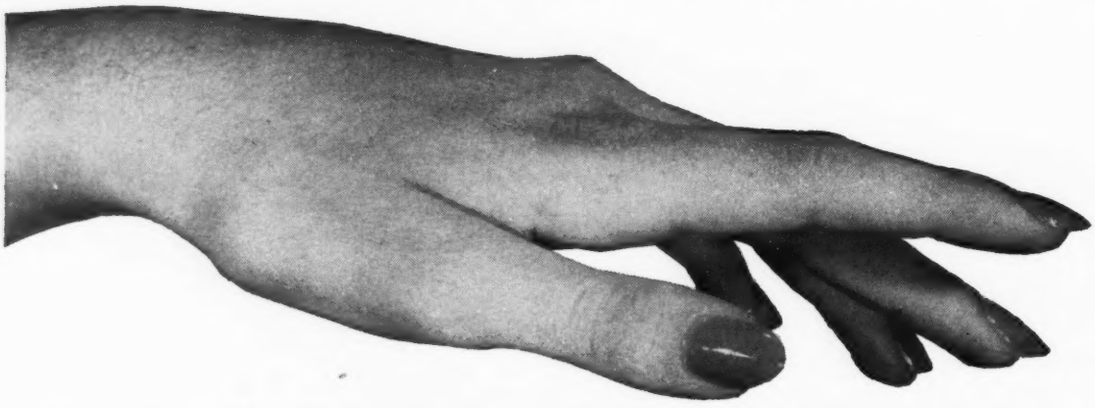
Clinico-pathologic Conference

Special Feature

Case Report

From Youth to Age

Benzestrol Covers Your Estrogenic Problems



"Benzestrol, in my experience, provides prolonged beneficial effects . . . . Undesirable side reactions, . . . were not encountered in my experience . . . In general also there seemed to be quite a decided improvement in the vague arthropathies and hypertensions associated with the menopausal syndromes."*

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Available in all Dosage Forms:

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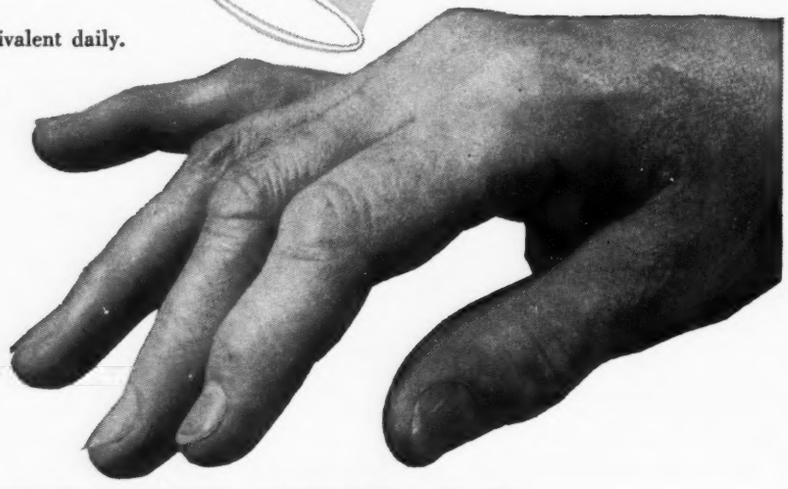
Vaginal Tablets: 0.5 mg.
Injectable Solution: 5.0 mg. per cc.
Elixir: 2.0 mg. per teaspoonful.
Average Dose: 1 to 2 mg. or equivalent daily.

*Hufford, A.R.: J.A.M.A., *123*, 259, (1943)



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2, 4 - di (p - hydroxyphenyl) - 3 - ethyl hexane
Clinical abstracts, literature and samples on request.

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a practical *step forward* in the therapy of rheumatic affections

Pabalate usually provides better therapy for rheumatic affections than pure salicylate itself, through its mutually synergistic combination of para-aminobenzoic acid and salicylate.[1,2] Reports of authoritative clinical tests show a *higher* degree of pain relief... to *more* patients... on *lower* dosage... over *longer* periods... with *greater freedom* from adverse reactions.[3]

REFERENCES: 1. Dry, T. J. et al.: Proc. Staff Meetings Mayo Clin., 21:497, 1946. 2. Hoagland, R. J.: Am. J. Med., 9:272, 1950. 3. Smith, R. T.: J. Lancet, 70:192, 1950.

FORMULA: Each enteric-coated tablet or each teaspoonful of chocolate-flavored liquid contains 0.3 Gm. (5 gr.) sodium salicylate U.S.P., and 0.3 Gm. (5 gr.) para-aminobenzoic acid (as the sodium salt).

A. H. ROBINS CO., INC.
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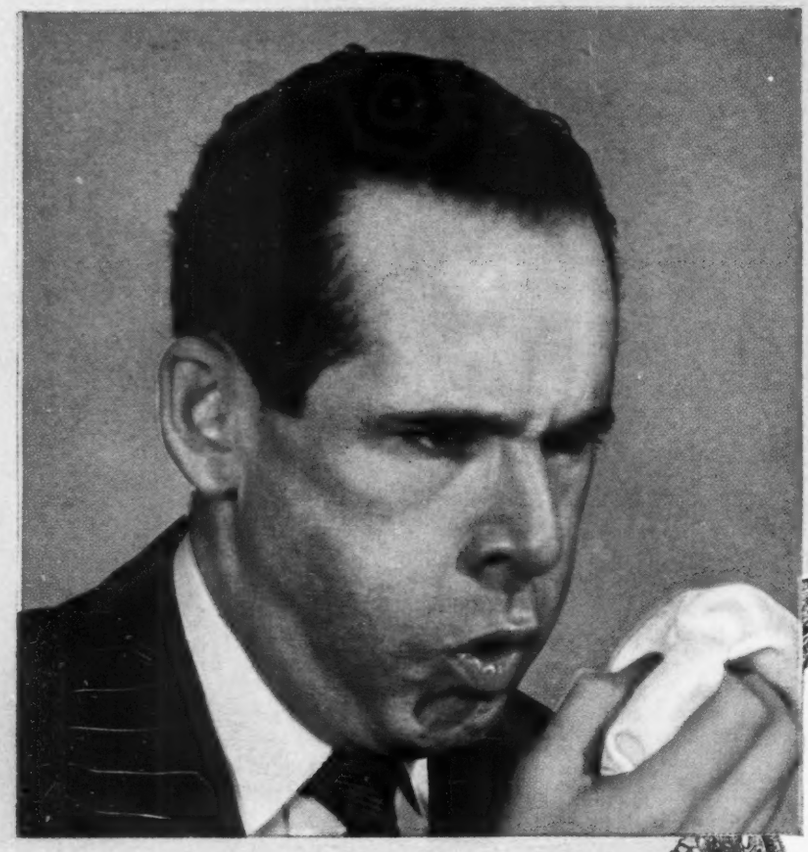
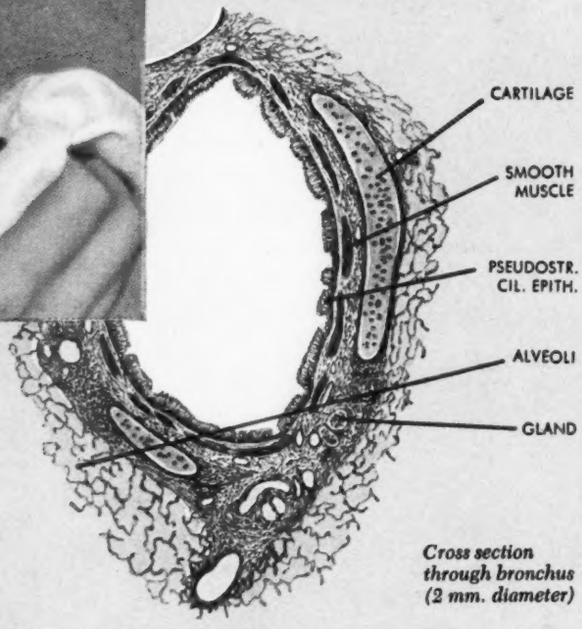
Robins **Pabalate®**

Seven Years' Research that opened a **New Era**

in Cough Therapy





Cross section through bronchus (2 mm. diameter)

The time encrusted *empirical* approach to cough therapy—with its "picture of confusion, contradiction and neglect"[2]—can now be replaced by sound, *rational* non-narcotic treatment, thanks to the pioneering studies of Boyd et al.,[1,2] demonstrating that glyceryl guaiacolate is the most powerful of expectorants commonly used. Robitussin—the antitussive-expectorant with specific drug action—provides glyceryl guaiacolate for increasing respiratory tract fluid, together with desoxyephedrine, for its bronchial-spasm-relieving[3] and its mood-improving actions—in an aromatic syrup that is highly patient-acceptable.

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Robitussin®

promotes useful cough...
minimizes harmful cough

References:

1. Boyd, E. M. and Lapp, S.: J. Pharmacol. and Exper. Therap., 87:24, 1946. 2. Connell, W. F. et al.: Canad. M.A.J., 42:220, 1940. 3. Novelli, A. and Tainter, M. L.: J. Pharmacol., 77:324, 1943.

Formula:

Each 5 cc. (1 teaspoonful) contains 100 mg. glyceryl guaiacolate and 1 mg. desoxyephedrine hydrochloride, in a palatable aromatic syrup.

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SOLGANAL®

(aurothioglucose)

BIBLIOGRAPHY (1) Holbrook, W. P.: New York Med. (no. 7) *4*:17, 1948. (2) Ragan, C., and Boots, R. H.: New York Med. (no. 7) *2*:21, 1946. (3) Rawls, W. B.; Gruskin, B. J.; Ressa, A. A.; Dworzan, H. J.; and Schreiber, D.: Am. J. M. Sc. *207*:528, 1944.

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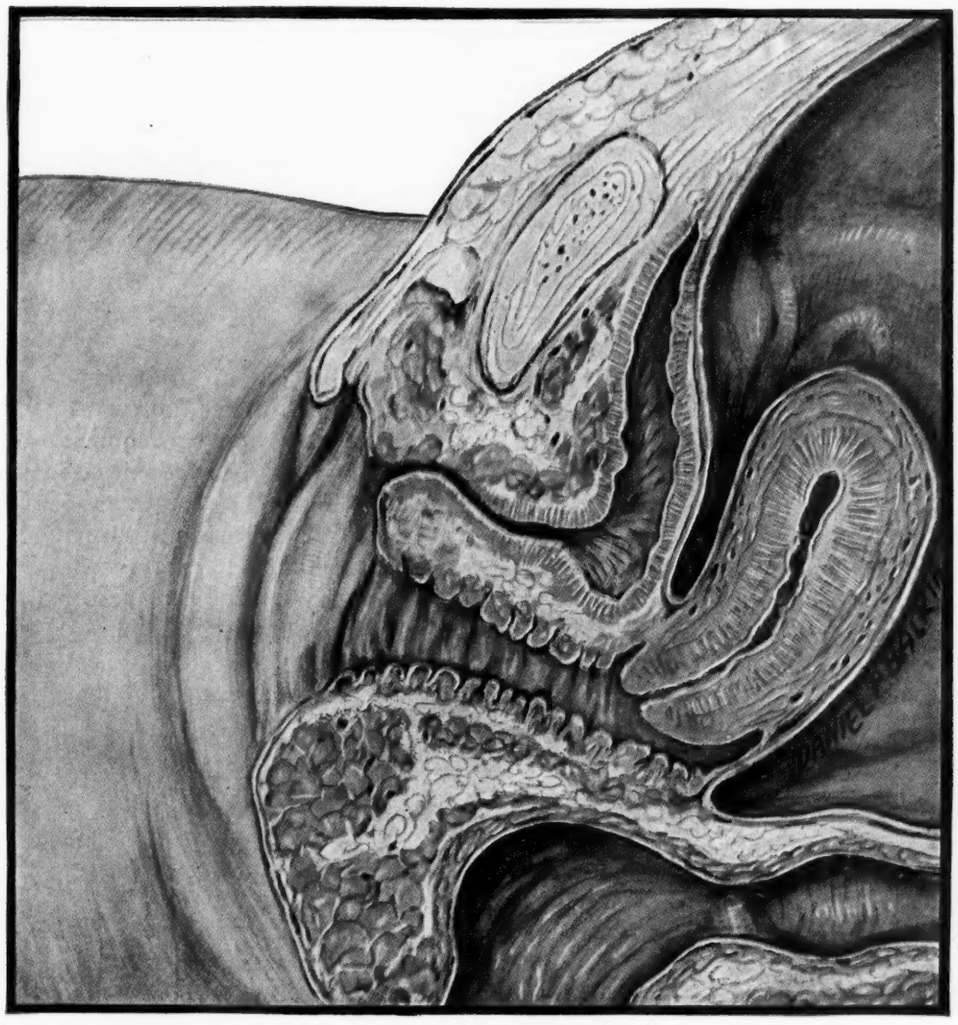

"The thin, grey, foamy discharge associated with excoriation of the labia and vagina, strawberry spots on the cervix, and intense itching almost always means trichomoniasis. Trichomonas is associated with a mixed bacterial flora, but not necessarily with a purulent discharge."

Passmore, G. G.: Treatment of Discharges from the Vagina in Private Practice, North Carolina M. J. 11:487 (Sept.) 1950.

floraquin® —aims at restoring and maintaining a normal vaginal environment unfavorable to the growth of pathogenic organisms. Floraquin contains Diodoquin-Searle (diiodohydroxyquinoline), a potent trichomonacide and fungicide, combined with lactose, dextrose and boric acid adjusted to effect the reestablishment of the normal vaginal pH and, in turn, the normal flora. G. D. Searle & Co., Chicago 80, Illinois.

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In Gonorrheal Infections

Prompt response to Terramycin "low-dosage schedule"[1]

of 26 cases treated with a single 1 Gm. dose
(4 capsules, 250 mg. each)
23 were cured (smear and culture negative) in 24 hours,
3 re-treated with 0.5 Gm. q. 6 h. 3 x responded
in 24 hours.

"All 26 patients were still symptom free and well one week from the time of starting treatment."[1]

Terramycin

rapidly absorbed

"... produces significant continuous blood levels when 250 mg. are given every six hours."[2]

well tolerated

"... side-effects have not constituted a problem in therapy."[3]

Supplied: 250 mg. capsules, bottles of 16 and 100;
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50 mg. capsules, bottles of 25 and 100.

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in the menopause:

new zest for life, new joy in living

Alone or in conjunction with estrogenic therapy, 'Benzebar'—combining 'Benzedrine' Sulfate and phenobarbital—is highly effective in controlling the neurotic symptoms of the menopause.

The 'Benzedrine' in 'Benzebar' restores optimism, cheerfulness and sense of well-being; imparts a feeling of energy and alertness. Simultaneously, the phenobarbital relieves tension, nervous excitability and agitation. And, combined in Benzebar, the beneficial effects of both drugs seem to be more than additive: they are enhanced. Better results are achieved than can be expected with either drug alone.

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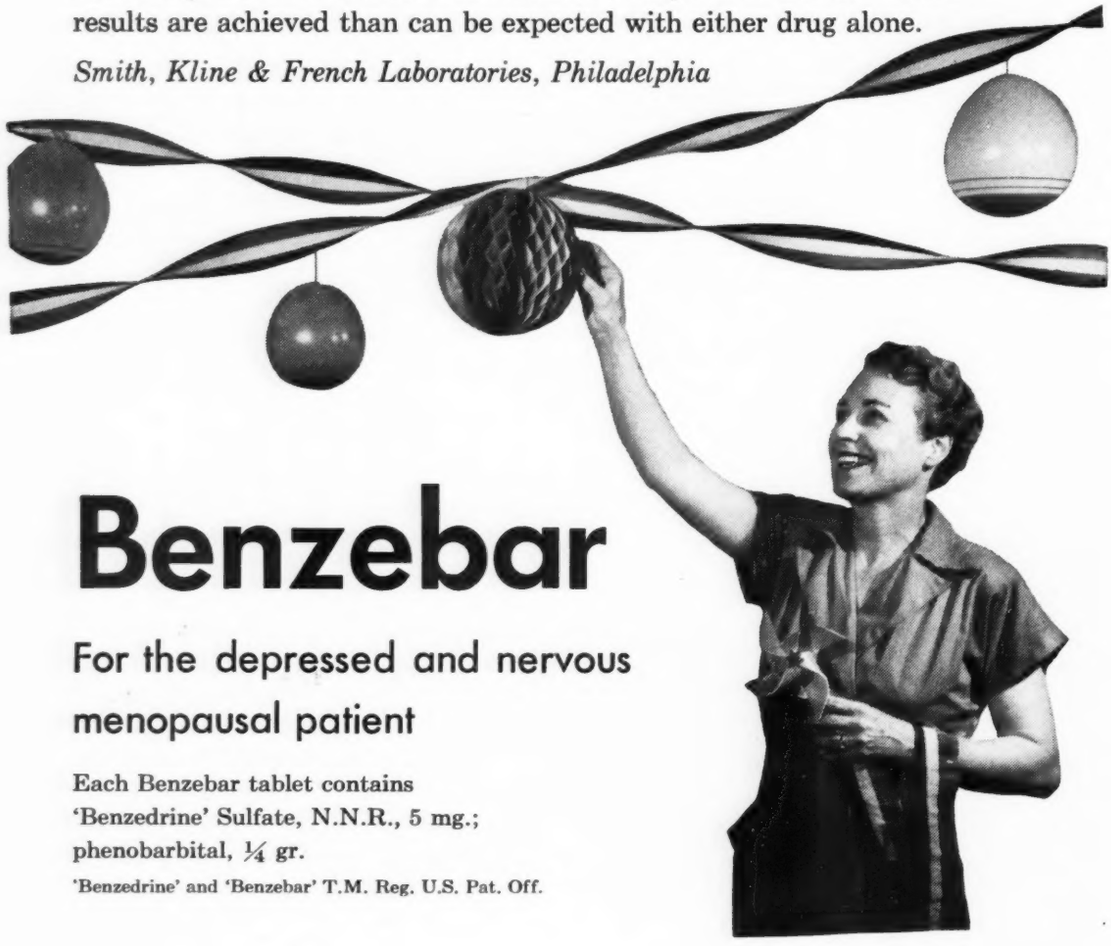

Benzebar

For the depressed and nervous menopausal patient

Each Benzebar tablet contains
'Benzedrine' Sulfate, N.N.R., 5 mg.;
phenobarbital, ¼ gr.

'Benzedrine' and 'Benzebar' T.M. Reg. U.S. Pat. Off.

New....

New LOW PRICES

New TABLET POTENCIES

A Substantial Saving to Your Patients Receiving....

VERILOID*

IN THE TREATMENT OF HYPERTENSION

The excellent acceptance accorded Veriloid by the profession, and the construction of expanded manufacturing facilities have made possible a substantial reduction in the price of this unusual hypotensive agent.

Veriloid is now available in 3 tablet potencies: 1.0 mg., 2.0 mg., and 3.0 mg. Based on former prices, the 1.0 mg. tablet is now available to your patient at a saving of 16⅔%, the 2.0 mg. tablet at a saving of 25%, and the 3.0 mg. tablet at a saving of 33⅓%.

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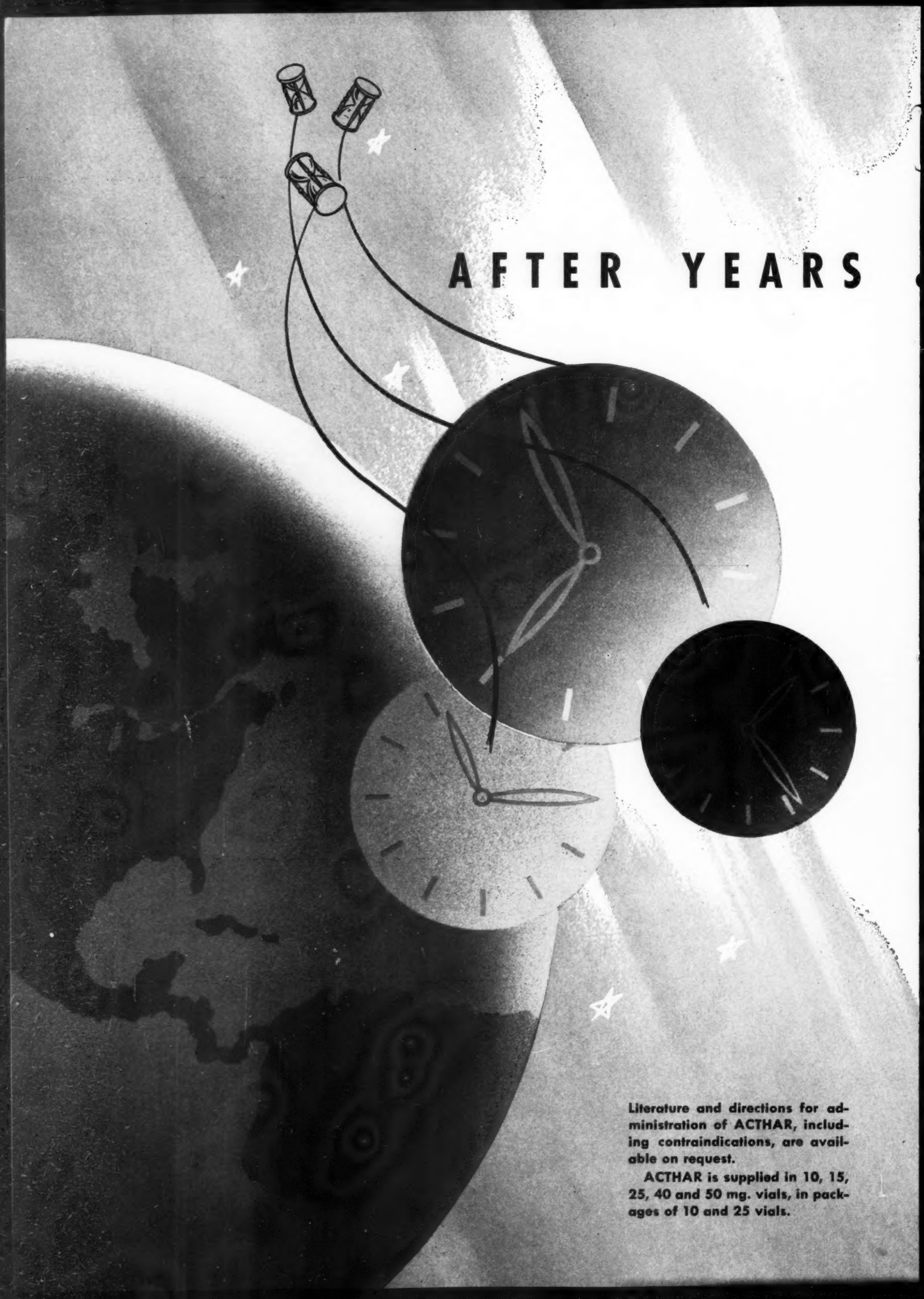

Literature and directions for administration of ACTHAR, including contraindications, are available on request.

ACTHAR is supplied in 10, 15, 25, 40 and 50 mg. vials, in packages of 10 and 25 vials.

. . . hours

Reversal of heretofore intractable diseases beginning within hours after instituting ACTHAR therapy, is the culmination of years of intensive research by The Armour Laboratories, together with independent investigators.

✔ ACTHAR, the first adrenocorticotropic hormone made available to the physician, represents the physiologic stimulus for the adrenals to produce and discharge the complete spectrum of cortical hormones.

Virtual absence of cumulative effects permits precise, yet flexible, dosage schedules. The exclusive utilization of physiologic mechanisms for its powerful therapeutic action furthermore contributes to the clinical safety of ACTHAR.

ESTABLISHED INDICATIONS: Collagen diseases or connective tissue diseases, such as rheumatoid arthritis, rheumatic fever, acute lupus erythematosus; hypersensitivities, such as severe asthma, drug sensitivities, contact dermatitis; most acute inflammatory diseases of the eye; acute inflammatory conditions of the skin, such as acute pemphigus and exfoliative dermatitis; inflammatory conditions of the intestinal mucosa, such as ulcerative colitis; and metabolic diseases, such as acute gouty arthritis and secondary adrenal cortical hypofunction.

ACTHAR

ARMOUR LABORATORIES BRAND OF ADRENOCORTICOTROPIC HORMONE (A. C. T. H.)

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PHYSIOLOGIC THERAPEUTICS THROUGH BIOCHEMICAL RESEARCH

When the diagnosis is Pyelitis

First:

consider

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CHEMISTRY
AMERICAN MEDICAL ASSOCIATION

to establish
and maintain
urinary antisepsis...

To establish and maintain urinary antisepsis, MANDELAMINE* is many times preferred because it is quickly effective against the organisms most commonly encountered in urinary-tract infections. Its exceptional freedom from untoward reactions and its wide range of antibacterial activity commend it for use as soon as the diagnosis has been made.

Urinary antisepsis is often achieved in uncomplicated pyelitis in as few as three days. Speedy recovery is thus secured in many cases without necessitating higher-cost therapy.

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for nourishment!

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Concentrated!

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nutrient powder

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CARBOHYDRATE	derived from cane, milk and grain sugars and soybean 20 Gm.
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LIVER	Whole liver substance, together with other natura factors of the vitamin B complex, including vitamin B_{12} 1 Gm.

DELMOR is a new and exceptionally useful formula for supplementing presurgical, obstetric, or convalescent diets with highest quality whole protein and other essential nutrients. A deliciously flavored powder, DELMOR may be given cooked or uncooked, with any kind of food, or between meals. Supplied in 1-lb. and 5-lb. bottles. Literature and recipes on request. Sharp & Dohme, Philadelphia 1, Pa.

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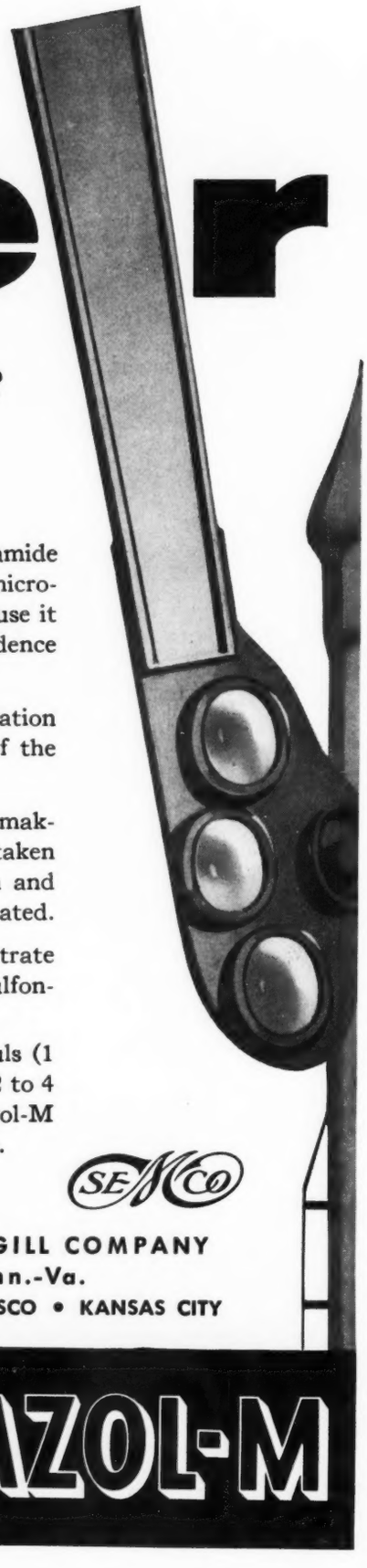
in Sulfonamide Therapy



Aldiazol-M brings a high degree of safety to sulfonamide therapy. This alkalizing suspension of equal parts of microcrystalline sulfadiazine and sulfamerazine is safer because it decreases the danger of crystalluria and reduces the incidence of allergic reactions. It offers these advantages:

Greater Efficacy, achieved through decreased acetylation of the absorbed sulfonamides, and rapid absorption of the microcrystalline form.

Highly Palatable. Aldiazol-M is pleasantly flavored, making it acceptable to virtually all patients. It is readily taken by children, making for universal patient cooperation and permitting its use whenever sulfonamide therapy is indicated.

Greater Urinary Solubility is produced by sodium citrate which increases urinary solubility of the combined sulfonamides by more than 400%.

The maintenance dose of Aldiazol-M is 2 teaspoonfuls (1 Gm. of total sulfonamides) every 4 hours; initial dose, 2 to 4 teaspoonfuls (3 to 6 Gm. of total sulfonamides). Aldiazol-M is available at all pharmacies in pint and gallon bottles.

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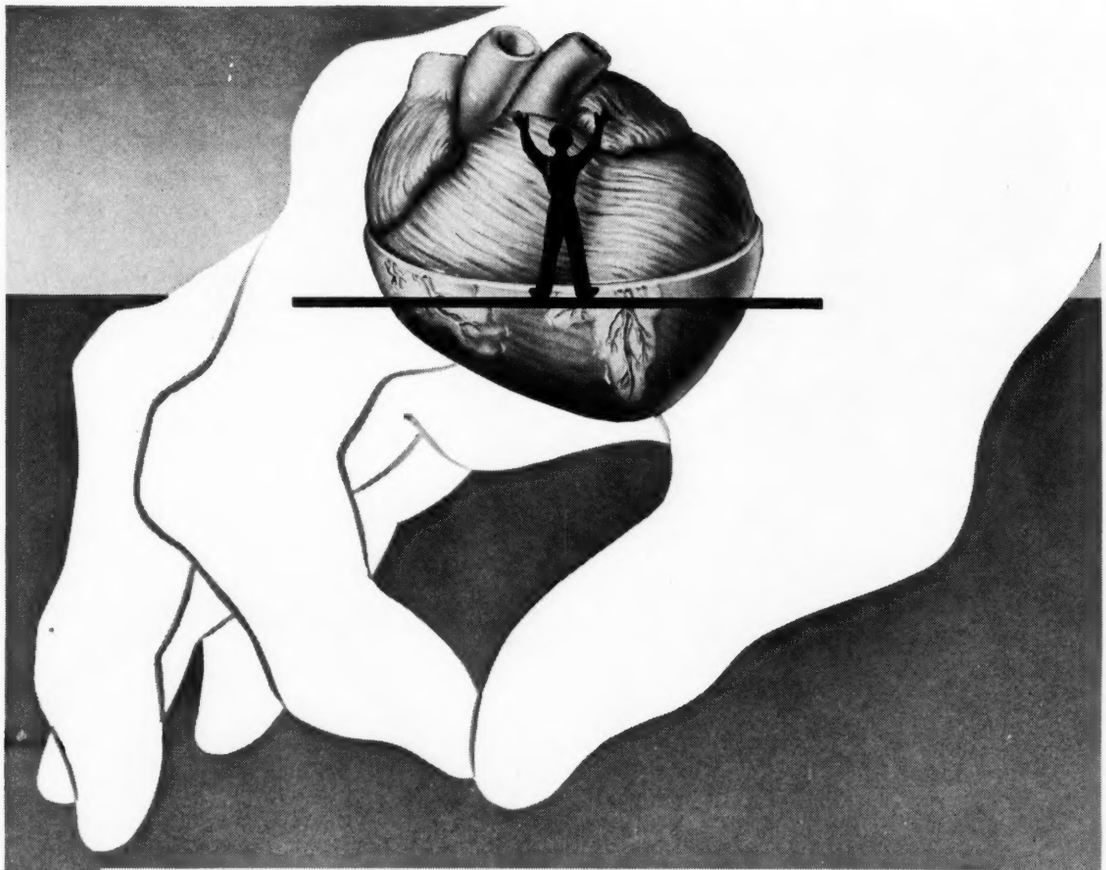
Formula

Each teaspoonful (5 cc.) of Aldiazol-M contains:

Sulfadiazine (microcrystalline)	0.25 Gm.
Sulfamerazine (microcrystalline)	0.25 Gm.
Sodium Citrate	1.0 Gm.

ALDIAZOL-M



HIGHER NEW ANTIRHEUMATIC THERAPY *SALICYLATE LEVELS* VITAMIN C PROTECTION

Pabasyl Tablets represent a new concept in antirheumatic therapy with the salicylates. Each enteric-coated tablet supplies:

Para-Aminobenzoic Acid* ...0.3 Gm. (5 grains)
Sodium Salicylate .....0.3 Gm. (5 grains)
Ascorbic Acid .....0.01 Gm. (10 mg.)

Pabasyl Tablets afford rapid relief of pain, fever and inflammation in many rheumatic diseases because they provide:

1. **HIGHER Salicylate Levels** — With simultaneous administration, Paba and salicylates have a reciprocal action that increases salicylate concentration in the blood.

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3. **Vitamin C Protection** — Ascorbic acid maintains Vitamin C levels often depleted by fever and salicylate therapy.

Enteric coating allays gastric irritation.

**As the Sodium Salt.*

pabasyl
In Bottles of 100 Tablets.

Dosage adult: 2 tablets three times a day.

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FOR URINARY TRACT INFECTION

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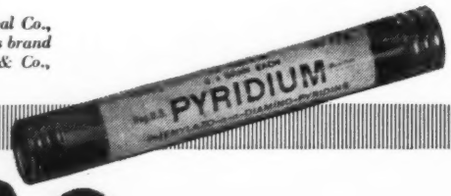
Gratifying Relief

from distressing symptoms

The action of orally administered Pyridium often enables patients to carry on without interruption of normal pursuits throughout the course of specific treatment of uncomplicated cystitis, urethritis, and pyelonephritis.

This effective urinary analgesic relieves distressing symptoms such as urinary frequency and pain and burning on urination, without systemic sedation or narcotic action.

Pyridium is the trade-mark of Nepera Chemical Co., Inc., successor to Pyridium Corporation, for its brand of phenylazo-diamino-pyridine HCl. Merck & Co., Inc. sole distributor in the United States.



The complete story of Pyridium and its clinical uses is available upon request.

Pyridium®

(Brand of phenylazo-diamino-pyridine HCl)

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in intractable peptic ulcer

KUTROL®

UROENTERONE, PARKE-DAVIS

PEPTIC ULCER INHIBITANT

when other therapy fails

Beneficial response in up to 70 to 80 per cent of cases —
Noteworthy results in chronic cases of Duodenal and Jejunal Ulcers having frequent recurrences and resistant to intensive conventional therapy.

Remission of ulcer often within 3 to 6 weeks —
Rapid relief of symptoms and disappearance of ulcer crater.

Simplified regimen —
Normal three-meals-a-day schedule soon after treatment begins.

Well-tolerated —
Does not inhibit gastric secretion. No toxicity or idiosyncrasy noted.

DOSAGE: Two KUTROL Kapseals® four times daily, one-half hour before mealtime and at bedtime.

PACKAGING: KUTROL Kapseals®, 75 mg., are supplied in bottles of 100.

Descriptive Literature Available On Request.

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MEDICAMENTA VERA

The physician knows

. . . but the patient too seldom appreciates . . . that

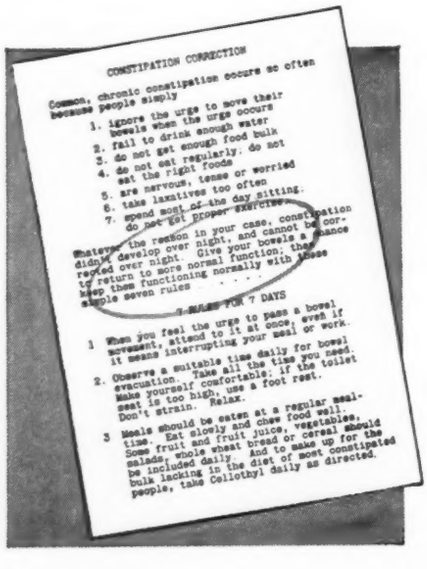
constipation cannot be corrected overnight

The "improper habits of living and eating"[1] which cause constipation are not formed overnight. Once deeply ingrained, such habits are not easily changed – and constipation becomes more difficult to correct.

An aid to patient-education:

In a simple leaflet, "7 Rules for 7 Days", the patient is asked to *give his bowels a chance to return to more normal function.* The leaflet is designed specifically for patient-instruction and clearly outlines an easy-to-follow, physiologically correct regimen for better bowel hygiene.

Available to physicians: Pads of the "7 Rules" may be had on request. Simply write "7 Rules" on a prescription blank and send to Chilcott Laboratories, Morris Plains, New Jersey.



CONSTIPATION CORRECTION

Common, chronic constipation occurs so often because people simply

1. ignore the urge to move their bowels when the urge occurs
2. fail to drink enough water
3. do not get enough food bulk
4. do not eat regularly, do not eat the right foods
5. are nervous, tense or worried
6. take laxatives too often
7. spend most of the day sitting, do not get proper exercise.

Whatever the reason in your case, constipation didn't develop over night, and cannot be corrected over night. Give your bowels a chance to return to more normal function, then keep them functioning normally with these simple seven rules . . . .

7 RULES FOR 7 DAYS

1 When you feel the urge to pass a bowel movement, attend to it at once; even if it means interrupting your meal or work.

2. Observe a suitable time daily for bowel evacuation. Take all the time you need. Make yourself comfortable; if the toilet seat is too high, use a foot rest. Don't strain. Relax.

3 Meals should be eaten at a regular meal-time. Eat slowly and chew food well. Some fruit and fruit juice, vegetables, salads, whole wheat bread or cereal should be included daily. And to make up for the bulk lacking in the diet of most constipated people, take Cellothyl daily as directed.

An aid to physiologic correction:

Cellothyl, physiologically correct bulk, may be prescribed in the therapeutic management of constipation.

Consistently good results reported in clinic and private practice

In obstinate clinic-treated cases,[1] it was found that even a lifetime of constipation *can be corrected in a matter of days* with Cellothyl. Additional studies showed that of habitually constipated patients treated in private practice, 80 to 92% obtained "good" to "excellent" results.[2,3] These investigators concluded that Cellothyl (physiologically correct hydrophilic colloid) is a valuable addition to a well-planned anticonstipation program, particularly where poor dietary and bowel habits of long standing are not easily remedied.

Time SAVED in patient-instruction

The constipated patient often is conditioned to expect prompt purgation. However, when normal intestinal function is described and the "simple rules of bowel hygiene"[3] explained, the patient better understands the difference between mere temporary relief and actual correction. The leaflet "7 Rules for 7 Days" will help your patient realize that overnight correction is virtually impossible—and will also serve as a daily reminder of your instructions. Copies are available on request.

Time NEEDED for physiologic correction

Constipation correction with Cellothyl requires time because Cellothyl acts in an *unhurried, physiologic manner*. Adequate time (12 to 36 hours) must be allowed for it to pass through the digestive tract to the colon and rectum before the first normal bowel movement can be expected. Cellothyl follows the normal digestive gradient and passes through the stomach and small intestine in a fluid state; then thickens to a smooth gel in the colon to provide bulk where bulk is needed for soft, moist, easily passed stools. With adequate bulk assured, the patient may "in the course of a few days . . . be able to resume more normal bowel habits."[4]

Dosage: 3 Tablets t.i.d., each dose with a full glass of water until normal stools pass regularly. Then reduce to minimum levels for as long as required. *Daily fluid intake must be high.* *To wean the "cathartic addict"*, administer for several days ½ the usual dose of cathartic together with Cellothyl, then ¼ the usual dose, then Cellothyl alone for as long as necessary. Cellothyl is not habit-forming and does not cause rebound constipation.

Are you using the "7 Rules" for constipation correction?

1. *Bargen, J. A.: Gastroenterology* 13:275, 1949.

2. *Musick, V. H.: J. Oklahoma M. A.* 43:360, 1950.

3. *Schwcig, K.: New York State J. Med.* 48:1822, 1948.

4. *Council on Pharmacy and Chemistry: J.A.M.A.* 143:897, 1950.

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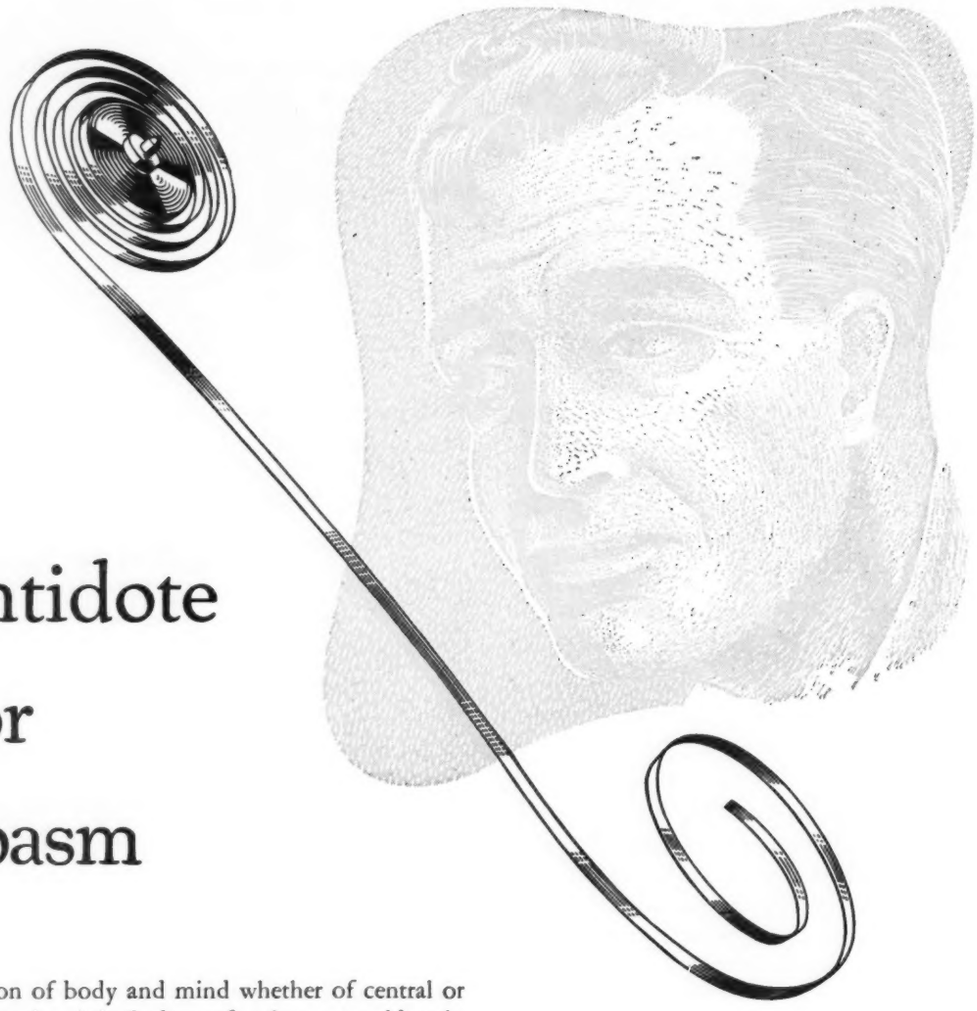

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...and with extremely low toxicity

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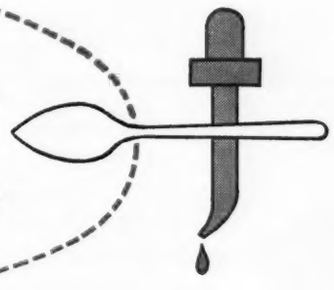

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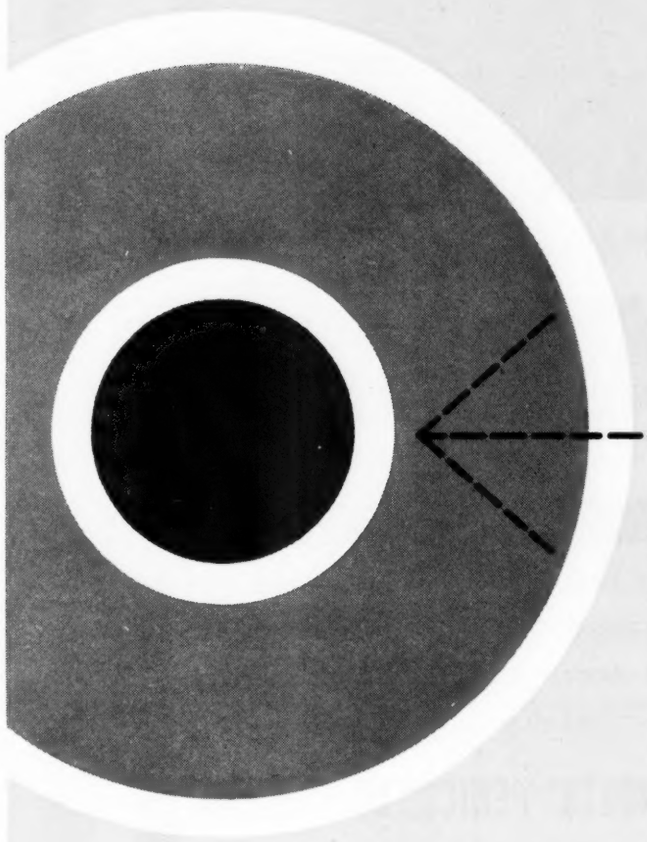

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bibliography: (1) Donovan, M. A.: New York State J. Med. *45*:1756, 1945. (2) Reaser, P. B., and Burch, C. E.: Proc. Soc. Exper. Biol. & Med. *63*:543, 1946. (3) Griggs, D. E., and Johns, V. J.: California Med. *69*:133, 1948. (4) Chapman, D. W., and Schaffer, C. F.: Arch. Int. Med. *79*:449, 1947. (5) Modell, W.; Gold, H., and Clarke, D. A.: J. Pharmacol. & Exper. Therap. *84*:284, 1945. (6) Finkelstein, M. B., and Smyth, C. J.: J. Michigan M. Soc. *45*:1618, 1946. (7) Gold, H., and others: Am. J. Med. *3*:665, 1947.

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The American Journal of Medicine

VOL. X JANUARY, 1951 No. 1

In Memoriam: Walter Walker Palmer

WALTER Walker Palmer, who was among many other things Chairman of the Advisory Board of *The American Journal of Medicine* since its inception, died on October 28, 1950. It is altogether appropriate that simple tribute be paid to this great man in these pages.

Dr. Palmer was born February 27, 1882, on a farm in Southfield, Massachusetts, the scion of parents of fine New England stock, Henry Wellington Palmer and Almira Roxana (Walker) Palmer. Prepared at Mt. Hermon Academy he attended Amherst College where he won distinction both as scholar, winning his Phi Beta Kappa key, and as athlete, playing varsity football. After receiving the B.S. degree at Amherst in 1905 and following a brief period of teaching mathematics at Milton Academy he entered Harvard Medical School from which he graduated in 1910. Upon completion of his internship at the Massachusetts General Hospital in 1912 he held a Henry P. Walcott Fellowship and an instructorship in physiologic chemistry at Harvard Medical School, initiating important studies in acid-base balance and edema formation in nephritis under the aegis of Professor L. J. Henderson. From 1913 to 1915 Dr. Palmer served as Resident Physician at the Massachusetts General Hospital, and from 1915 to 1917 as Assistant Resident Physician at the Hospital of the Rockefeller Institute. In 1917 he was appointed Associate Professor of Medicine at Columbia University and Acting Director of the Medical Service of the Presbyterian Hospital. Two years later he was made Associate Professor of Medicine at Johns Hopkins University and Associate Visiting Physician to the Johns Hopkins Hospital.

In 1921, having abundantly demonstrated his outstanding capacity and leadership, Dr. Palmer was invited to become head of the Department of Medicine by four leading American medical schools. It was a difficult choice but his course was clear. Disdaining greater emoluments and established prestige Dr. Palmer elected to accept the full time position of Bard Professor of Medicine at Columbia University and Director of the Medical Service of the Presbyterian Hospital because of his abiding faith in the full time system of medicine and in the establishment of the first Medical Center, to which Columbia University was committed. For the next twenty-six years until his retirement in 1947 to become Director of the Public Health Research Institute of the City of New York Dr. Palmer devoted his major energies to fulfillment of these two ideals which he held to be in the best interests of the development of American medicine. Time has long since proved his wisdom.

Dr. Palmer's earlier research activities, carried out in collaboration with L. J. Henderson and D. D. van Slyke, led to classic studies on acid-base equilibrium which are still cited in current publications in this field; the Henderson and Palmer method for estimating titratable acidity of the urine, which appeared in 1914, is even now in general use. He also made significant contributions to the mechanisms of ketosis, particularly in diabetes, and to iodine metabolism in the normal and abnormal thyroid gland, anticipating many later developments in this field. He participated in the first demonstration of the usefulness of radioactive iodine in some cases of thyroid carcinoma. These studies were all characterized by insight into basic mechanisms of disease and by sound experiment.

Dr. Palmer was a member of many professional societies. He was elected to the presidency of the Harvey Society and of the

American College of Physicians. He served for twenty-eight years as member, subsequently Vice-Chairman, of the Council on Pharmacy and Chemistry of the American Medical Association, helping to shape its policy. He was a member of the National

Walter Walker Palmer 1947.

Board of Medical Examiners from 1921 to 1943. During World War II he served as Chairman of the Committee on Drugs and Medical Supplies of the National Research Council and was a member of its Committee on Medicine. He was an Advisor to the War Production Board and a member of the Advisory Committee of the Office of Scientific Research and Development. In 1945 and 1946 he was Chairman of the Medical Advisory Committee appointed by Vannevar Bush to prepare a report for the President on the establishment of a National Science Foundation. He was awarded the honorary degree of Doctor of Science from Amherst College in 1922, from Columbia University in 1929 and from Princeton in 1949.

Dr. Palmer served well for many years as a member of the editorial board of *Archives of Internal Medicine* and of *Medicine*. At the time of his death he was Editor-in-Chief of the Nelson Loose-Leaf System of Medicine and Chairman of the Advisory Board of *The American Journal of Medicine*. Characteristic of the man was the part he played in the founding of this Journal. He was astute in anticipating the need for a teaching journal of this type when few others appreciated that need; he was courageous in committing himself and some of his closest friends to the Editorial Board of the new and uncertain venture; he was invariably kind in encouraging and assisting the inexperienced Editor through the early struggles of organization; he was firm in insisting on the highest plane of integrity in policy; and, altogether typical of the man, he could be persuaded only with the greatest difficulty to accept public recognition of his role as Chairman of the Advisory Board.

Dr. Palmer was first and foremost a man of integrity, of principle and character, with a strong sense of moral responsibility for the public welfare. He had a quiet dignity which at once inspired confidence and respect. He was a kindly man, sympathetic and understanding of the frailties of mankind and of the needs of his patients, the members of his department, his students, his friends, of all those who sought his help and advice. His gentle humor, his wide interests even in the simplest activities of the humblest person endeared him to all who knew him. He loved to work with his hands, whether in the laboratory, the garden or at the carpenter's bench. He was a generous man, always ready to sacrifice his personal advantage. He was completely devoid and intolerant of ostentation. He was a discerning man, his mind penetrating to fundamental issues, seeing everything in proper perspective, gifted with most uncommon common sense. He was like a solid rock in troubled waters; to come to him for help was like setting foot on dry land after a long sea voyage. His spirit shall endure in the model Department of Medicine he built up at Columbia University, in the forward course of American medicine which he did so much to chart, in the many younger men in medicine whose character he helped to mold.

ALEXANDER B. GUTMAN, M.D.

Clinical Studies

Clinical Variations in Primary Atypical Pneumonia*

WILLIAM S. JORDAN, JR., M.D., ROBERT W. ALBRIGHT, M.D.,
FRENCH H. MCCAIN, M.D. *and* JOHN H. DINGLE, M.D.
Cleveland, Ohio

CLINICAL studies of primary atypical pneumonia as observed in military and college personnel[1–13] have indicated the variations in clinical patterns seen in these relatively homogeneous groups. In older age groups the presence of other pathologic changes, such as cardiovascular disease, often alters the clinical manifestations and renders the problem of differential diagnosis even more difficult. It is the purpose of this report to describe primary atypical pneumonia as seen in a general hospital and thereby to provide additional clinical and laboratory data to aid in the recognition of this disease and in the future evaluation of new therapeutic agents. An attempt has been made to illuminate further some of the many facets of atypical pneumonia, especially the correlation of symptoms and of signs with the roentgenologic findings. Finally, these three variables have been correlated with the pattern of the serologic changes.

MATERIAL AND METHODS

The cases in this series, with the exception of a ten year old child, were adult patients admitted to University Hospitals, Cleveland, during the nine-month period from August, 1947, to May, 1948. Daily observations were made by the same recorders, using check sheets. Total leukocyte and differential counts were performed on admission and, in most cases, every two days thereafter. Sputa and throat cultures were examined for common respiratory pathogenic bacteria, mouse inoculation being used to detect pneumococci. Aerobic blood cultures were made on admission and later as indicated. Roentgenograms, including lateral views, were taken on admission and at least every seven days thereafter. Sera were drawn on admission and weekly thereafter for as long as the patients were available. Cold hemagglutinin and streptococcus MG agglutinin tests were performed, using the technics summarized by Feller;[14] a fourfold or greater change in titer was considered to be significant.

The diagnosis of primary atypical pneumonia was made when the following criteria were met: (1) pulmonary infiltration shown by roentgenogram; (2) a compatible clinical course and (3) absence of bacteria as causative agents. Of forty patients treated with penicillin or sulfonamides, none showed any response to these agents.

A total of seventy-five cases was studied. When subjected to critical review, eight cases were rejected from subsequent analyses for the following reasons: (1) Bacterial causation could not be definitely eliminated in two cases. (2) Three patients had heart disease and it was impossible to state that cardiac failure did not account for all of the clinical findings. (3) In one case the findings were confused by a previous thoracoplasty. (4) One patient had an unusual migratory pulmonary infiltration of six months' duration and a diagnosis was not established. (5) One patient returned to his home out of state, and an adequate follow-up to exclude tuberculosis was not possible.

RESULTS

Age and Sex. The sixty-seven cases consisted of nineteen males and forty-eight females ranging in age from ten to seventy-

* From the Departments of Preventive Medicine and of Medicine, School of Medicine, Western Reserve University, and the University Hospitals, Cleveland, Ohio. This investigation was supported in part through the Commission on Acute Respiratory Diseases, Army Epidemiological Board, Office of The Surgeon General, U. S. Army, and by grants from the Brush Foundation, the Cleveland Foundation, the S. P. Fenn Trust, and Mr. Philip R. Mather.

eight years. The average age of the male patients was 39.8 years and of the females 39.4 years. Fifty-two per cent of the patients were between thirty and fifty years of age; 10 per cent were over the age of sixty.

TABLE I
NATURE OF SYMPTOMS AT ONSET IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

Symptoms	Cases	
	No.	Per cent
Upper respiratory	18	27
Lower respiratory	18	27
Constitutional	20	30
Lower respiratory and constitutional	7	10
Other combinations	4	6
Total	67	100

Symptoms. The average duration of symptoms before admission to the hospital was ten days. The onset was gradual in the majority of patients. The first symptoms of illness as experienced by each patient were grouped as "upper respiratory" (nasal discharge, sore throat), "lower respiratory" (cough, chest pain, dyspnea) and "constitutional" (headache, feverishness, malaise). Table I shows that the initial symptoms fell in these three categories with about equal frequency; that is, equal numbers of patients had onsets resembling a common cold, or tracheobronchitis or "grippe." The daily occurrence of these symptoms in all cases in relation to day of illness is shown in Figure 1. Constitutional and lower respiratory symptoms were most prevalent on about the eighth or ninth day of illness. In contrast, upper respiratory symptoms when present occurred largely at the onset of the illness and became less prevalent as the disease progressed. In those individuals with such symptoms the average duration of upper respiratory symptoms was nine days, of constitutional symptoms seventeen days and of lower respiratory symptoms twenty days.

The chief complaints of the patients at the time of admission were: cough, 61 per cent; malaise, 16 per cent; and fever, 13 per cent. (Table II.) The frequency of occurrence of symptoms at any time during the illness is also shown in Table II. All except two patients experienced cough. Almost all of the patients had fever, malaise and sore throat.

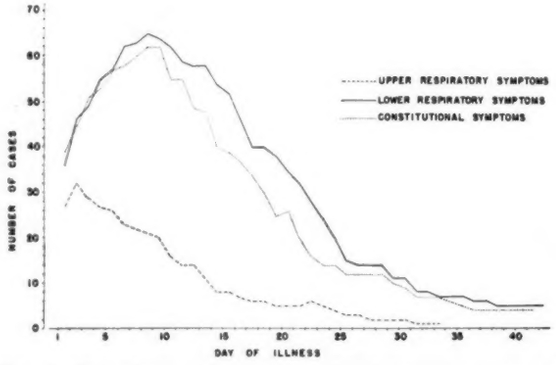

FIG. 1. Prevalence of symptoms in sixty-seven cases of primary atypical pneumonia by day of illness.

Approximately 75 per cent complained of chilliness, anorexia and headache. Substernal discomfort was experienced somewhat more frequently than pleural pain. For the purposes of analysis the term pleural pain included any pain, usually sharp in nature, which was related to respiration and was located in an area other than the sternal region. When pleural pain occurred

TABLE II
SYMPTOMS IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

Symptoms	Chief Complaint		Frequency of Symptoms	
	No.	Per cent	No.	Per cent
Cough	41	61	65	97
Malaise	10	15	63	94
Fever	9	13	63	94
Sore throat	1	2	62	93
Chilliness			50	75
Anorexia			49	73
Headache			49	73
Nasal congestion			22	33
Nausea			20	30
Substernal pain			17	25
Pleural pain	2	3	14	21
Dyspnea			13	19
Vomiting	1	2	12	18
Shaking chill			6	9
Sneezing			3	5
Leg pain	2	3	2	3
Hemoptysis	1	2	1	2

it was always mild. Shaking chills were experienced by six patients.

Although not usually a serious illness from the point of view of mortality, primary atypical pneumonia assumes considerable importance in terms of duration and subsequent prolonged convalescence. In this series the total duration of illness averaged 23.6 days, with a range of seven to fifty-two days, as calculated from the initial symptom to the time of discharge from the hospital.

TABLE III
TIME OF MAXIMUM TEMPERATURE, DURATION OF FEVER AND DURATION OF ABNORMAL PULMONARY SIGNS IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

Days of Disease	Maximum Temperature*		Duration of Fever*		Duration of Pulmonary Signs†	
	No.	%	No.	%	No.	%
0–7	21	31	4	6	3	5
8–14	31	46	27	40	13	20
15–21	10	15	22	33	21	31
22–28	2	3	5	7	18	27
29–35	0	..	4	6	5	7
36–42	2	3	3	5	2	3
>42	0	..	1	1	3	5

* One patient was afebrile during period of hospitalization.

† Two patients had no abnormal pulmonary signs.

Vital Signs. The temperature on admission varied from normal to 41.4°C., with an average of 38.8°C. One patient was afebrile during the period of observation. In 66 per cent of the cases the highest temperature recorded was between 38° and 40°C.; in 31 per cent the temperature exceeded 40°C. Maximum temperatures recorded after admission occurred on the average on the eleventh and twelfth days of disease. Three-fourths of the patients experienced their maximum temperatures during the first two weeks of illness and 91 per cent attained their febrile peaks by the twenty-first day. (Table III.) Almost one-half of the patients were afebrile by the end of the second week of illness and 79 per cent by the end of the third week. The type of fever curve was sustained in half and remittent in half of the cases. Resolution occurred by lysis in 85 per cent of the cases and by crisis in 15 per cent.

The pulse rate was between 100 and 135 in 73 per cent of the cases, with only four patients having a rate greater than 135. Fourteen patients, 21 per cent, had a normal rate at all times. On the basis of a rise of two beats per minute for each degree (F.) rise of temperature, 69 per cent of the patients had a relative bradycardia.

TABLE IV
PHYSICAL FINDINGS IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

Physical Findings	Cases	
	No.	Per cent
Fine rales	61	91
Pharyngitis	40	60
Dullness	39	58
Diminished breath sounds	37	55
Coarse rales	30	45
Rhinitis	23	34
Bronchial breath sounds	16	24
Dyspnea	14	21
Cyanosis	8	12
Abdominal distention	5	7
Pleural friction rub	2	3

Physical Signs. Table IV shows the number of cases in which each physical sign was found. Moderate redness of the pharynx was present in 60 per cent. One-third showed redness, swelling and discharge in the nasal passages. On admission 22 per cent had no abnormal pulmonary signs but eventually abnormal signs were found in all except two cases. The most consistent finding was fine rales, observed in sixty-one, or 91 per cent. Dullness, diminished breath sounds and coarse rales each occurred in approximately one-half. Bronchial breath sounds were heard in sixteen, or 24 per cent; pleural friction rubs were rare, occurring in only two cases. Cyanosis and abdominal distention were present only in severely ill patients, and the latter was a stubborn complication when it occurred.

The period of time during which abnormal pulmonary signs persisted ranged from three to fifty-two days after onset, with an average for the group of twenty-one

days. But 42 per cent of the patients had persistent signs for more than three weeks after onset and 15 per cent for more than four weeks. (Table III.) The extremes were exemplified by the two patients who had no abnormal pulmonary signs and by a third

signs or symptoms of decompensation. Two days before admission she noted anorexia and headache, developed a slight cough and dyspnea. The next day she was chilly and feverish, and her cough became productive of yellow, blood-streaked sputum.

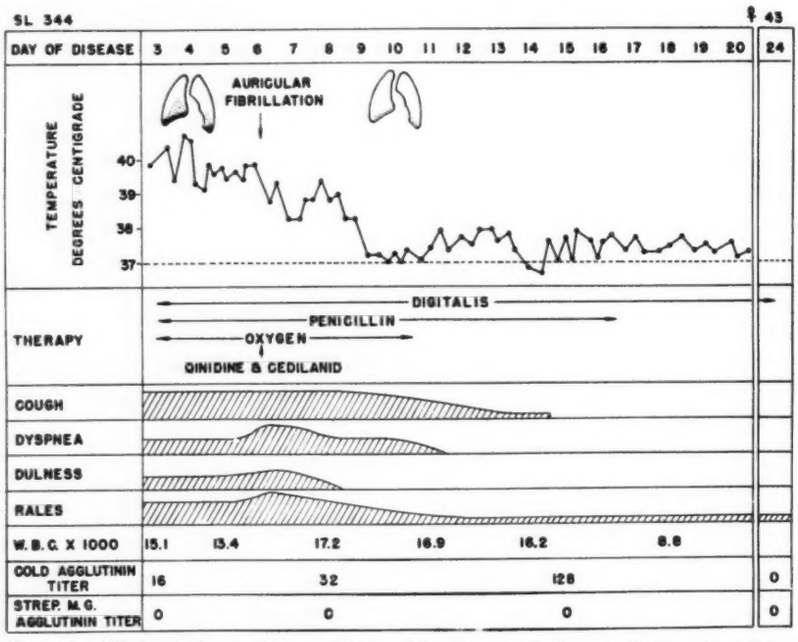

FIG. 2. Clinical chart of a patient with rheumatic heart disease in whom auricular fibrillation and congestive failure developed for the first time during a course of primary atypical pneumonia.

patient who had a few rales at the time of discharge on the fifty-second day of illness.

In the presence of other disease processes which could in themselves produce fever and abnormal pulmonary signs, the diagnosis of primary atypical pneumonia was difficult. It has long been recognized that intercurrent respiratory infections may have an adverse effect in individuals with limited cardiac reserve, the added burden imposed by the infection initiating arrhythmias and decompensation. Further, circulatory collapse, or "medical shock," was a common occurrence in the severe bacterial pneumonias. That primary atypical pneumonia may similarly affect the cardiovascular system is illustrated by the following cases:

CASE REPORTS

CASE I. A forty-three year old white housewife (Fig. 2) had had rheumatic heart disease with mitral stenosis for twenty years with no

Examination showed a temperature of 39.8°C., pulse 118, respirations 28 and blood pressure 140/92 mm. Hg. She was acutely ill, weak, dyspneic, slightly cyanotic and suffered paroxysms of coughing. There were dullness, bronchial breathing and pectoriloquy at the right lung base. No rales were heard. The left border of cardiac dullness was just inside the left anterior axillary line and the right border of dullness was 3 cm. to the right of the sternum. The rhythm was regular. A presystolic murmur was present at the apex and P_2 was accentuated. The leukocyte count was 15,150 per cu. mm., with 41 per cent segmented neutrophiles, 52 per cent unsegmented neutrophiles and 7 per cent lymphocytes. The initial throat and sputum cultures and two subsequent sputum cultures disclosed no pathogenic bacteria. Aerobic cultures of blood and pleural fluid showed no growth. The titer of cold hemagglutinins rose from 16 to 128. The initial roentgenogram of the chest showed dense, hazy shadows in both lung bases, much more marked on the right, and was interpreted

as indicating passive hyperemia, pleural fluid and pneumonia. The heart was enlarged and showed straightening of the left border consistent with rheumatic disease with mitral stenosis.

The patient was placed in an oxygen tent and given 50,000 units of penicillin intramuscularly every three hours. Digitalization had been completed prior to hospitalization and maintenance digitoxin was continued. On the second hospital day many rales, both fine and coarse, were audible at both lung bases, dyspnea was more severe and distention developed. The next day, the sixth of disease, her temperature was still 39.5°C. and she appeared extremely toxic. Her pulse suddenly became rapid and grossly irregular, and an electrocardiogram confirmed the diagnosis of auricular fibrillation. At this time, moist rales predominated in the lung bases and there was 3 + albuminuria. Intravenous cedilanid induced a reversion to normal sinus rhythm. She was continued on quinidine and given mercurial diuretics. The temperature fell by lysis to normal on the tenth day of illness, pulmonary findings gradually cleared and a repeat roentgenogram demonstrated satisfactory resolution of the pneumonia and possibly minimal passive hyperemia. A few fine rales could still be heard at both lung bases at the time of her discharge on the twenty-fourth day of her disease.

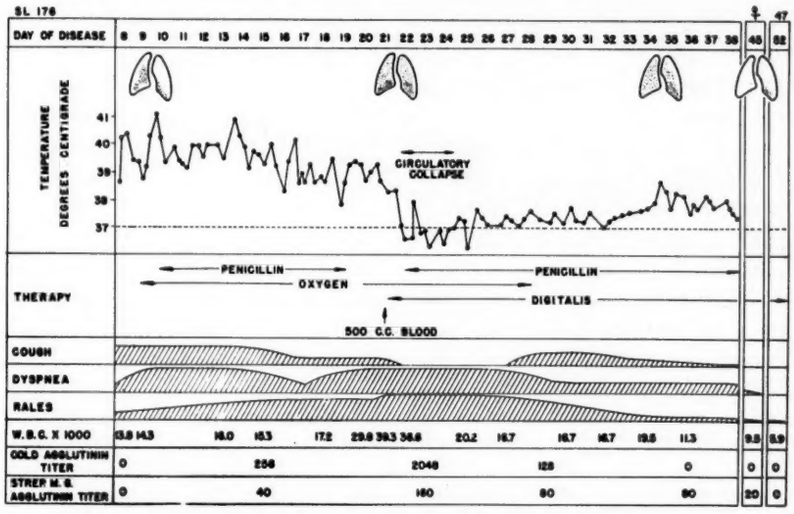

FIG. 3. Clinical chart illustrating the occurrence of circulatory collapse during the course of severe primary atypical pneumonia.

Comment. There was debate during this patient's illness as to whether congestive failure alone might not explain all of the clinical picture. However, her history was initially that of an acute respiratory infection. She became ill during an outbreak of respiratory disease in her family, and both she and her son developed elevated cold hemagglutinin titers. It would appear, rather, that the occurrence of atypical pneumonia was a sufficient insult to induce auricular fibrillation and congestive failure in a patient with previously compensated rheumatic heart disease.

CASE II. A forty-seven year old white housewife noted the gradual onset and progression for seven days of malaise, fever, sweats, chilliness, headache and paroxysmal cough productive of scanty, white sputum. (Fig. 3.)

On admission her temperature was 38.7°C., pulse 90, respirations 25 and blood pressure 130/80 mm. Hg. She was obese, appeared moderately ill and had a paroxysmal cough. The remaining abnormal physical findings were diffuse pharyngeal injection, pinpoint cryptic tonsillar exudate and pulmonary signs. There were minimal dullness, suppression of fremitus and breath sounds, and fine crepitant rales over the right base and fine rales over the right upper lobe anteriorly. The cardiovascular examination was normal.

Urinalyses showed 1 to 3+ albumin during the febrile stage, eventually clearing. The erythrocyte count was 3,760,000 per cu. mm. and the hemoglobin 69 per cent, declining to 2,200,000 and 55 per cent, respectively, during hospitalization. There was no evidence of hemolysis. The leukocyte count was 13,000 with 86 per cent neutrophiles, subsequently rising to

39,300 with 90 per cent neutrophiles. Initial bacteriologic studies revealed no respiratory pathogens; subsequent sputa revealed few to moderate numbers of hemolytic staphylococcus aureus. Admission cold hemagglutinin and streptococcal MG agglutinin titers were <4 and <10, respectively, rising in parallel manner to 2048 and 160, respectively, on the twenty-third day of disease. The admission roentgenogram showed patchy areas of peribronchial infiltration throughout the right lung.

In the first twenty-four hours the patient became rapidly worse. She developed cyanosis, abdominal distention, rising pulse and respiratory rates, increasing toxicity and a febrile rise to 41°C. She was placed in an oxygen tent and, in addition to symptomatic treatment, intramuscular penicillin was instituted. For the next seven days she remained severely ill. Her pulmonary signs spread gradually to involve the entire lung area except the apical portion of the left upper lobe. These signs consisted of rales only, with no other evidence of consolidation. On the fifteenth day of illness symptomatic improvement began and her fever started downward although her pulmonary signs remained unchanged. Penicillin was discontinued after 22 million units had been given in ten days without detectable effect. For the next three days her fever continued to resolve by lysis. However, her pulse and respirations gradually rose to 140 and 40, respectively. She began to have asthmatic-like attacks of dyspnea which responded well to parenteral aminophyllin. After three weeks of illness, because of the progressive anemia and its possible contribution to the tachycardia and tachypnea, 500 cc. of whole blood were given intravenously over a four-hour period. Immediately following the completion of the transfusion the patient became markedly cyanotic and dyspneic, with a respiratory rate of 50, and her pulse rose to 160. She was rapidly digitalized with cedilanid intravenously and digitoxin orally, intramuscular penicillin was reinstituted and atropine hypodermically was given. Periods of circulatory collapse appeared with cold clammy sweats, cold pallor of extremities and hypotension. Her temperature remained at subnormal levels of 36°C. Her leukocyte count rose to 39,300 with 90 per cent neutrophiles. Her obesity and the necessity for using portable roentgenograms precluded accurate evaluation of any change in heart size. These roentgenograms showed multiple nodular areas of an alveolar type of infiltration, conglomerate at the bases, throughout all lung fields, with no evidence of atelectasis or of infarction. Repeated electrocardiograms revealed only sinus tachycardia and digitalis effect. After forty-eight hours the patient rallied and her temperature rose to febrile levels again. Thereafter she pursued a prolonged but progressive convalescence. On the twenty-eighth day of disease the rales first began to diminish and the oxygen tent was discontinued. Her fever resolved slowly by lysis during the next two weeks and penicillin was again discontinued after 15 million units had been given. She was discharged on the fifty-second day of disease with slight residual infiltration at the left base by roentgenogram and a few rales in the same area.

Comment. This case represents a very prolonged and severe illness with no great discrepancy between signs, symptoms and roentgenograms on admission or during her course. In addition, the adverse effect of such a severe illness on an apparently normal cardiovascular system is illustrated. On admission no previous history or physical stigmata of cardiac decompensation or decreased reserve were apparent. After eleven days of a severe febrile pulmonary illness there were signs of possible cardiovascular damage. With the stimulus of an intravenous transfusion, gross manifestations of vascular collapse dramatically appeared.

Not only may atypical pneumonia aggravate or precipitate cardiovascular dysfunction but the pneumonia may be unrecognized and thereby lead to clinical confusion.

Case III. A seventy-eight year old white male was admitted complaining of cough, fever, frequency and nocturia. (Fig. 4.) He had had exertional dyspnea for ten years and intermittent ankle edema for several months. He was first seen in University Hospitals three years previously, at which time diagnoses of benign prostatic hypertrophy and chronic cystitis were made. He subsequently received two courses of sulfonamide because of recurrent pyuria. Two weeks before entry a cough began, at first dry and later productive of blood-tinged sputum. The cough increased, and anorexia, dyspnea

and malaise developed. A roentgenogram taken before admission showed cardiac enlargement and emphysema with passive hyperemia. He then noted chilliness and fever, and frequency and nocturia recurred.

units, was given intramuscularly every three hours. These measures caused little improvement. The pyuria gradually cleared but his temperature continued to range from 38° to 39°C. The rales persisted and nineteen days after

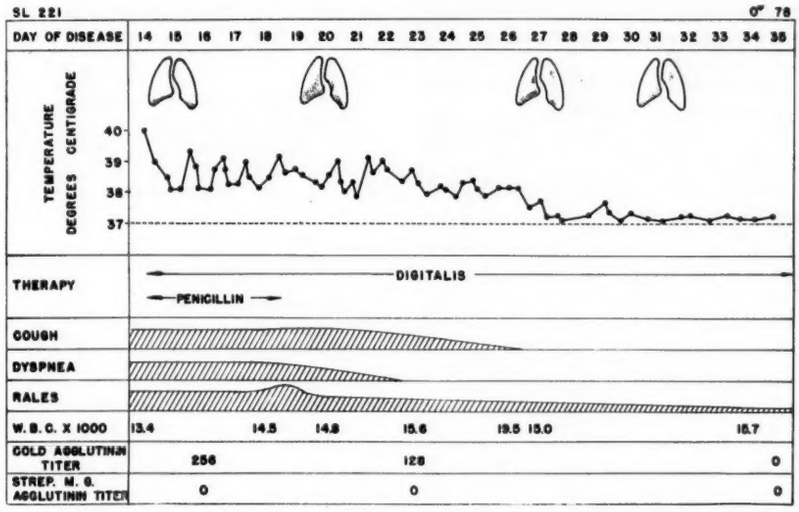

FIG. 4. The rales and fever in this elderly patient were attributed to cardiac decompensation and cystitis until the diagnosis of primary atypical pneumonia was confirmed by a change in cold hemagglutinin titer.

Examination showed an elderly, orthopneic male with a temperature of 40°C., pulse 85, respirations 20 and blood pressure 140/80 mm. Hg. The peripheral and fundal vessels were sclerotic. There was no distention of the neck veins. The left border of cardiac dullness was 2 cm. outside the mid-clavicular line in the sixth interspace. The rhythm was regular; no murmurs were heard. Numerous moist, coarse rales were heard at both lung bases and a few rales were heard over the left upper lobe posteriorly. The liver edge was questionably palpable at the right costal margin. The prostate was symmetrically enlarged and slightly tender. There was no peripheral edema.

Laboratory studies showed many pus cells in the urine and a leukocyte count of 13,300 per cu. mm., with a normal differential distribution. The blood urea nitrogen was 15 mg. per ml. and a urea clearance test was normal. Cultures of the urine and blood showed no growth. A type 6 pneumococcus was recovered from the sputum by mouse inoculation. A roentgenogram of the chest showed cardiac enlargement and haziness of the costophrenic sinuses interpreted as passive hyperemia of the lungs.

He was placed on a salt-poor diet, digitalized and given mercurial diuretics. Penicillin, 30,000

onset a roentgenogram showed peribronchial infiltration in the left lower lobe. A cold hemagglutination test at this time showed 1+ agglutination in all tubes to a titer of 256. Fine rales then appeared over the right upper lobe and another film showed clearing of the infiltration in the left lower lobe and a few streaky shadows in the right second interspace. A week later cold hemagglutinins were definitely positive to a titer of 128, falling to < 4 in another two-week interval. The patient's temperature gradually returned to normal over a fourteen-day period, his dyspnea and cough lessened and only a few rales were audible at the left base at the time of discharge five weeks after onset.

Comment. This patient was initially considered to represent a case of decompensated arteriosclerotic heart disease with a urinary tract infection. But when conventional cardiac therapy failed to improve the pulmonary findings and urinary infection seemed inadequate as a cause of the fever, it became apparent that some other explanation had to be found. Primary atypical pneumonia was suggested by the migratory character of the pulmonary infiltration and confirmed by the change in cold hemag-

glutinin titer. This disease should be considered in any age group with confusing pulmonary findings.

Laboratory Results. The sputum was blood-streaked in 14 per cent of the patients but in no instance was it rusty or grossly bloody. Pneumococci were isolated from the sputa or throat cultures of eight patients. The types found were 6, 11, 14, 19, 27, 31 and 32. No beta-hemolytic streptococci were isolated and staphylococci were not found in significant numbers.

TABLE V

LEUKOCYTE COUNTS ON ADMISSION IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

Leukocyte Count	Stage of Disease						Average Neutrophile Count %
	1st wk.		2nd wk.		3rd wk.		
	No.	%	No.	%	No.	%	
<6,000	11	28	2	9	1	16	65
6-9,000	21	54	10	45	0	0	68
9–15,000	4	10	2	9	1	16	73
15-20,000	3	8	8	36	3	50	75
20–39,000	0	0	0	0	1	16	85
Total	39	100	22	100	6	100	

TABLE VI

COLD HEMAGGLUTININS AND STREPTOCOCCAL MG AGGLUTININS IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

	Cases	
	No.	Per cent
Cold hemagglutinins alone	19	29
Strep. MG agglutinins alone	5	7
Both	19	29
Neither	24	35
Total	67	100

The range of leukocyte counts on admission was from 4,000 to 25,000, with an average count of 9,000. The level of the initial leukocyte count rose in relation to the duration of disease. (Table v.) Forty-five, 69 per cent, of the patients had counts below 9,000 on admission. During the period of hospitalization, however, 66 per cent had counts over 9,000. In two cases leukocyte counts rose to 35,000 and 39,000. There was only a moderate polymorphonuclear response in the cases with the higher total leukocyte counts. Three cases had a normal leukocyte count while febrile followed by a leukocytosis with defervescence of fever. It was more common for the rise of the leukocyte count to accompany spread of the pulmonary lesion, as occurred dramatically in four of the five patients who had counts over 25,000 and in many other less marked instances. Pneumococci were found in the sputa of four of the forty-six cases with counts over 9,000 and in four of twenty-one cases without a leukocytosis.

TABLE VII

RELATIONSHIP OF DURATION OF FEVER TO THE DEVELOPMENT OF COLD HEMAGGLUTININS AND STREPTOCOCCUS MG AGGLUTININS IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

Duration of Fever—Days	No. of Cases	Cold Hemagglutinins		Strep. MG Agglutinins	
		No.	%	No.	%
0–7	5	0	0	1	20
8–14	27	11	41	8	30
15–22	21	15	71	10	48
>22	14	12	86	5	36

Serology. Fourfold or greater rises in titer either of cold hemagglutinins, of streptococcal MG agglutinins or both were demonstrated in forty-three, 65 per cent, of the patients. Cold hemagglutinin titers rose in 58 per cent; streptococcal MG agglutinin titers rose in 36 per cent. (Table VI.) An increase in streptococcal MG agglutinin titer unaccompanied by an increase in cold hemagglutinin titer was noted in five cases.

The presence of a rise in agglutinin titer and the height of such rise was related to the severity of the illness as measured by the duration of fever (Table VII) and the extent of pulmonary infiltration. (Table VIII.) The roentgenographic picture in the one case with involvement of five sectors

without agglutinin rises was that of diffuse, light peribronchial infiltration. In cases showing fourfold or greater rises in titer, the lowest titers were confined to cases with minimal involvement of one to two sectors. However, high titers were not invariably confined to cases with extensive roentgenographic involvement.

TABLE VIII

RELATIONSHIP OF THE EXTENT OF PULMONARY INFILTRATION TO THE DEVELOPMENT AND HEIGHT OF AGGLUTININ TITERS IN SIXTY-SEVEN CASES OF PRIMARY ATYPICAL PNEUMONIA

No. of Pulmonary Sectors Involved	No. Cases	Cold Hemagglutinins			Strep. MG Agglutinins		
		No.	%	Fold Increase*	No.	%	Fold Increase*
1	30	11	37	17	7	23	1.4
2	20	14	70	70	9	45	4.4
3	8	6	75	68	4	50	4
4	6	5	83	134	2	33	6
5	1	0	...	...	0	...	....
6	2	2	100	512	2	100	24

* The lowest dilutions titrated for cold hemagglutinins and streptococcus MG agglutinins were 1:4 and 1:10 respectively. These dilutions, if agglutinins were absent, were used to determine fold increases.

In the thirty-eight patients showing a fourfold or greater rise in cold hemagglutinin titer, the rises were detected between the seventh and twentieth days of disease in 87 per cent. In the twenty-four patients showing fourfold or greater rises in streptococcal MG agglutinins, the rises also were found between the seventh and twentieth days of disease in 70 per cent; in 30 per cent the rises did not occur until the fourth to fifth week of disease. Approximately one-quarter of the patients developed initial rises of streptococcal MG agglutinins at a time later than that noted for similar changes in cold hemagglutinin titers.

Further evidence on the frequency of the slower rise and fall of streptococcal MG agglutinins as compared to cold hemagglutinins was obtained by following the titers in the nineteen cases showing rises in titer of both agglutinins. A parallel rise occurred in thirteen, or 70 per cent, of these cases. In the remaining cases the rise of cold hemagglutinins preceded the rise of streptococcal MG agglutinins by one to two weeks. In no instance did the rise of streptococcal agglutinins antedate the rise of cold hemagglutinins. The course of the two agglutinin titers was parallel in only six of these nineteen cases. In thirteen cases the streptococcal MG agglutinin titer remained elevated longer than the cold hemagglutinin titer. When last tested, both agglutinin titers were still elevated in ten cases but the cold hemagglutinin titer was falling while the streptococcal MG agglutinin titer was rising. In three cases the cold hemagglutinin titer fell to normal fourteen to thirty-one days before the streptococcal MG agglutinin titer returned to normal.

Complement fixation tests for antibodies to Rickettsia burneti and the psittacosis-lymphogranuloma group of viruses were carried out with sera from these patients at the Army Medical Center through the kindness of Dr. Joseph E. Smadel. Although two or more specimens of sera were available from each of the patients, there were thirteen instances in which the last specimen was obtained between the tenth and thirteenth day of illness. None of the patients developed antibodies to Rickettsia burneti. In only two patients were antibodies found for viruses of the psittacosis group. One of these had a titer of 10 on the fourteenth day of illness and the other had a titer of 20 on the twenty-fourth day of illness. Neither showed a significant change in the titers of the acute and convalescent sera. Since antibodies to these agents may not develop until after the third week of illness, the significance of the negative results in thirteen of the patients is less than in the others. The absence of a history of exposure to birds, cattle or other animals, however, makes it unlikely that any of the illnesses was due to these agents.

A diagnostic rise in antibody titer to the influenza viruses A or B was not demonstrated in the sera from any of the patients.

Roentgenographic Studies. Prior to review-

ing the roentgenographic findings and before attempting any correlation of the roentgenograms with other variables, four types of roentgenographic picture were defined:[15] (1) *Bronchitic:* Increased size and density of one or both hilar shadows with prominent bronchovascular shadows extending out from the hilum. (2) *Peribronchitic:* Prominent bronchovascular markings extending from the hilum into the cardiophrenic sinuses and outward into the lung, together with peribronchial infiltration which still allowed the linear markings to be clearly visible through the infiltration. (3) *Alveolar:* Denser infiltration which obscured the peribronchial markings in its central portion. The size, shape, location and degree of density were variable. (4) *Lobar:* Dense consolidation suggesting a lobar type of consolidation.

The incidence of the four roentgenographic types was: bronchitic, forty cases, or 60 per cent; peribronchitic, forty-one cases, or 61 per cent; alveolar, thirty-three cases, or 49 per cent; lobar, seven cases, or 10 per cent. While the mildest form, bronchitic, was common, in only five cases was it the only type present throughout the course. One-half of the cases progressed to the alveolar form with easily recognizable consolidation. The type confused with pneumococcal lobar consolidation by roentgenogram was by no means rare, occurring in one out of every ten patients.

The distribution of the lesions was recorded by sectors and not by lobes, with each hemithorax being divided into three equal parts. Two or more sectors were involved in 57 per cent of the cases. The right and left lower sectors dominated, and equally so, with over 50 per cent on each side being affected. The two middle thirds were next most common, again equally, with 30 per cent on each side affected. However, the two upper sectors were not equally affected. Involvement of the right upper third was fairly common, being present in thirteen, or 20 per cent, of the cases; the left upper third was involved in only three cases. Six cases showed only unilateral upper sector infiltration, lesions difficult to differentiate from tuberculosis.

To examine the correlation between signs and roentgenograms three grades of severity or extent were defined. It was then possible, for example, to say that a given case had a minimal roentgenogram with moderate or extensive signs.

At the time of admission physical findings paralleled the roentgenographic infiltration in 52 per cent of the cases. In 25 per cent the roentgenogram revealed infiltration when there were no signs, or extensive infiltration when signs were minimal. This discrepancy persisted for as long as one week before the first signs appeared or became commensurate with the roentgenograms. In 18 per cent, conversely, signs were present and the roentgenograms normal, or signs were extensive when the roentgenographic involvement was minimal. This discrepancy persisted for as long as ten days before the roentgenograms first revealed infiltration or became commensurate with the signs. In three cases both abnormal signs and roentgenographic infiltration were absent on admission. Therefore, on admission roughly 50 per cent of the cases had parallel physical and roentgenographic findings. The other 50 per cent showed an obvious and marked discrepancy between signs and roentgenograms. In the latter group, although a few more cases exhibited predominance of the roentgenographic picture, almost as many cases exhibited the opposite phenomenon of the predominance of the signs.

As these cases were followed throughout their courses, early discrepancies tended to disappear. Fifty-seven cases, 85 per cent, eventually had courses in which the extent of the signs and roentgenographic changes were parallel. In ten cases the correlation between physical findings and the roentgenographic changes remained poor throughout the entire course. The great majority of this latter group fell into the category in which the signs spread widely and the roentgenographic picture remained the same or regressed.

The following case reports illustrate these extremes of correlation as observed on admission to the hospital, during the subsequent course, or both:

CASE IV. A twenty-seven year old white male (Fig. 5) noted for seven days the gradual onset and progression of malaise, aching, chilliness, fever, headache, sore throat and paroxysmal cough productive of moderate amounts of yellow, occasionally blood-streaked, sputum.

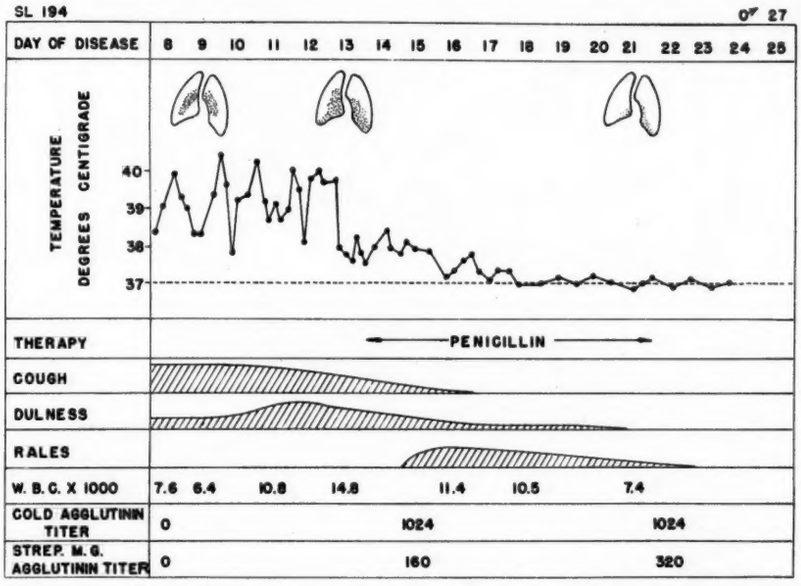

FIG. 5. A moderately severe case of primary atypical pneumonia in which pulmonary infiltration was extensive but abnormal physical signs were late in developing and minimal in extent.

On admission his temperature was 38.5°C., pulse 78, respirations 22. He appeared moderately ill and had a mild, paroxysmal cough. Aside from diffuse pharyngeal injection other abnormal physical findings were limited to the chest. Over the posterior superior section of the right lower lobe there was one small area of minimal dullness, suppressed fremitus and bronchovesicular breath sounds without rales. The leukocyte count was 7,600 with 80 per cent neutrophiles. The admission cold hemagglutinin and streptococcal MG agglutinin titers were <4 and <10, respectively, subsequently rising to 1024 and 320, respectively, on the twenty-second day of disease. The admission roentgenogram revealed extensive areas of dense alveolar type of infiltration occupying the right and left mid-lung fields.

In addition to symptomatic treatment he received 16.5 million units of penicillin intramuscularly after his temperature had begun to decline. The roentgenogram contrasted markedly with the few abnormal physical findings over the right hemithorax and the complete absence of abnormal signs over the left. Subsequent roentgenograms showed extension of the consolidation toward the bases. Not until the twelfth day of illness were definite signs of consolidation, without rales, apparent on the left side, and they were confined to the left hilar region. Not until the fifteenth day of disease were fine rales audible over this area. Thereafter, the roentgenographic resolution preceded by several days the resolution of the pulmonary signs.

Comment. This case of moderate illness demonstrated a marked discrepancy between findings by physical examination and by roentgenograms on admission. While pulmonary signs were present on admission, they indicated far less involvement than did the roentgenograms. This discrepancy persisted throughout the course. A parallel rise and course of agglutinin titers was observed.

CASE V. A thirty-four year old white female (Fig. 6) noted a sore throat and rhinitis two weeks before admission. Four days later she noted a pleuritic type pain in the left anterior chest but this disappeared within the next forty-eight hours. Fever, malaise, headache, hoarse-

ness and paroxysmal cough developed, increased in severity, and did not respond to sulfonamide or penicillin therapy.

On examination she appeared moderately ill with a temperature of 38.5°C., pulse 84, respirations 24 and blood pressure 164/105 mm. Hg. except in the apex posteriorly. Numerous rales and slight dullness were present over the left lower lobe. A roentgenogram at this time showed definite but still minimal peribronchial infiltration in both lower lobes. Her leukocyte count rose to 11,500 with no change in the differential count. By the twenty-third day of illness there were no signs of consolidation, the rales had decreased in number and the patient was afebrile.

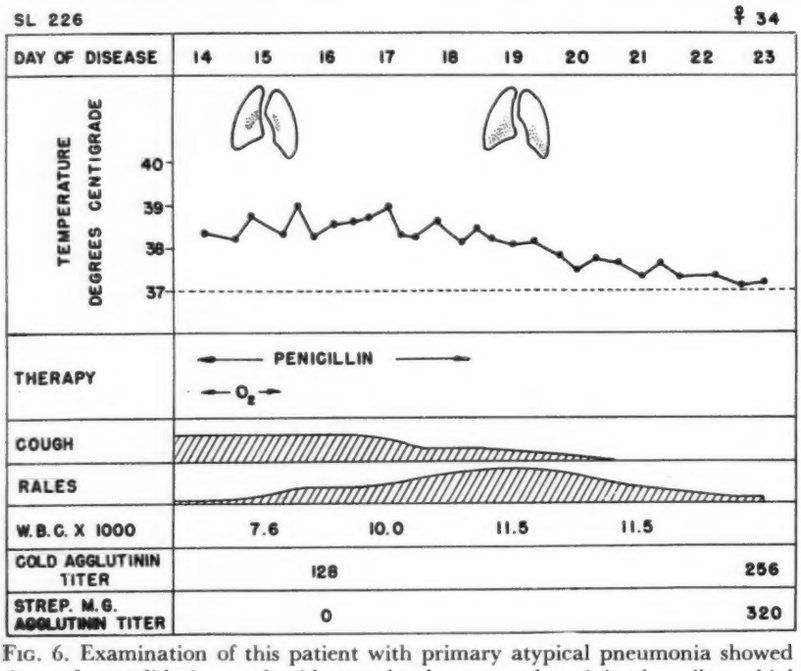

FIG. 6. Examination of this patient with primary atypical pneumonia showed signs of consolidation and widespread rales, yet only minimal peribronchial infiltration was demonstrated by roentgenogram.

Paroxysms of coughing produced greenish-yellow sputum. There was slight dullness, diminished breath sounds and crepitant rales over the right lung base. A few rales were heard over the left mid-lung field posteriorly and the right upper lobe anteriorly. The leukocyte count was 7,600 with 63 per cent neutrophiles. Throat and sputum cultures grew no pathogenic respiratory bacteria. An aerobic blood culture showed no growth. Cold hemagglutinins were present initially to a titer of 128, rising in a week to 256. Simultaneous streptococcus MG agglutinin titers were <10 and 320, respectively. The admission roentgenogram showed slight increase in the prominence of the bronchovascular markings in the right lung but no evidence of infiltration or consolidation.

She was placed in an oxygen tent for twenty-four hours and given penicillin, 40,000 units intramuscularly every three hours. Her temperature remained elevated, cough was troublesome and the rales continued to spread. By the fourth hospital day, the eighteenth day of disease, rales were present throughout the entire right lung

Comment. In this case all observers who listened to her chest were surprised at the extensiveness of the signs in view of the paucity of roentgenographic changes. Signs of consolidation and widespread rales were evident on physical examination yet only minimal peribronchial infiltration was demonstrated by roentgenogram. This case also showed an earlier appearance of cold hemagglutinins and a lag in the rise of the streptococcus MG agglutinins.

CASE VI. A forty-three year old nurse noted malaise and fatigue five days before admission. The next day chilliness and temperature of 38°C. developed. Two days before entry a dry, paroxysmal cough occurred associated with substernal discomfort and upper abdominal soreness. (Fig. 7.)

Examination showed a moderately ill female coughing frequently. Her temperature was 38.5°C., pulse 88, respirations 20 and blood pressure 122/70 mm. Hg. The pharynx was diffusely injected. There were slight dullness, diminished breath sounds and crepitant rales over the left mid-lung field posteriorly. The leukocyte count was 8,000 with 81 per cent neutrophiles. A type 11 pneumococcus was recovered from the sputum by mouse inoculation. An aerobic blood culture showed no growth. Cold hemagglutinin titers rose from <4 to 256. The admission roentgenogram showed peribronchial infiltration in the left perihilar region.

The patient was treated symptomatically for the first six days. Constitutional and respiratory symptoms then increased and rales became audible throughout the left lung and the right middle and lower lobes. The leukocyte count rose to 15,750. Dyspnea, cyanosis and abdominal distention were evident. She was placed in an oxygen tent and given 30,000 units of penicillin intramuscularly every three hours. A roentgenogram at this time showed "*resolution* of the infiltration in the left lung and increased vascular markings in the right upper lung field with no definite associated infiltration." The patient remained febrile, acutely ill and was kept in the oxygen tent for the next five days. By the twenty-second day of disease her temperature was normal and her leukocyte count had fallen to 6,800. The rales decreased in number but were still audible throughout the chest. She improved symptomatically except for a persistent cough, and a film on the twenty-seventh day of illness showed complete clearing.

Comment. At a time when this patient's disease was increasing in severity and physical examination indicated diffuse spread of the pneumonic process, roentgenograms not only failed to demonstrate progression of the lesion but actually showed beginning resolution. Both she and the previous patient exhibited leukocytosis coincident with the spread of their pneumonia.

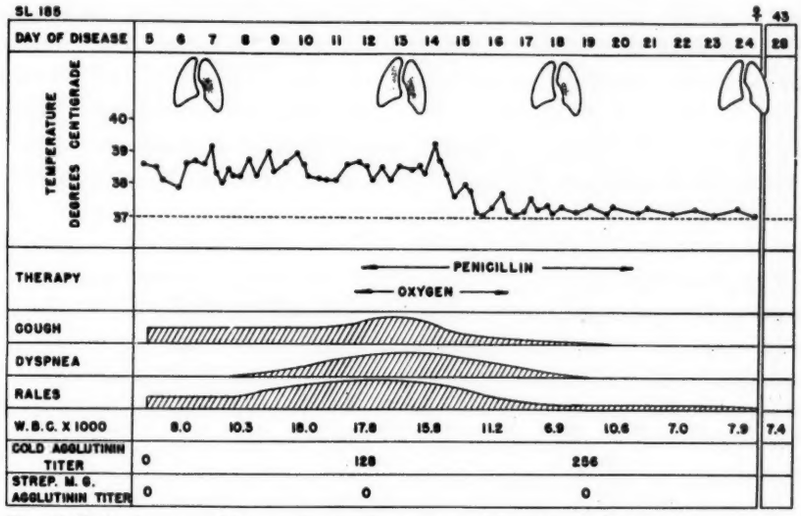

FIG. 7. Rales increased in number and extent as this patient's illness became more severe, but this spread was not demonstrated by roentgenogram.

COMMENTS

The patients in this series probably represent a sample of the more severe cases of primary atypical pneumonia occurring in the community. In addition to severity, the need for diagnostic aids in clarifying puzzling clinical pictures prompted hospitalization of a number of patients. When first seen, 50 per cent of the cases showed discrepancies between physical signs and roentgenographic findings. In the presence of additional pathologic processes such as rheumatic or arteriosclerotic heart disease, or emphysema, these discrepancies were further magnified and, as a result, the role of primary atypical pneumonia in the clinical picture was difficult to recognize. In the future the widespread use of new drugs

such as aureomycin, which has been effective in pneumococcal pneumonia[16] and may be effective in primary atypical pneumonia,[17–19] may mask the difference between bacterial and non-bacterial pneumonias. A knowledge of the variable clinical pattern of primary atypical pneumonia and a proper interpretation of laboratory results become essential for the recognition of this syndrome.

The initial symptoms of primary atypical pneumonia resembled those of a rhinitis, a bronchitis or "grippe" with equal frequency. Upper respiratory symptoms persisted for an average of nine days; constitutional symptoms and symptoms referable to the chest were present for seventeen and twenty days, respectively. The total incidence of symptoms corresponded to that previously reported.[2,4,13,20–27] The average patient was sick for ten days before hospitalization, experienced maximum temperature on the eleventh and twelfth days of disease and was afebrile by the seventeenth day. In the absence of effective therapy one-half of the patients were afebrile by the end of the second week of illness. Resolution by crisis occurred in 15 per cent of the cases. In these cases the use of a temperature response as an index of effective therapy would have been misleading. Since the more severe illnesses were characterized not only by persistent fever but also by spread of the pulmonary infiltration, the effectiveness of a therapeutic agent may be demonstrable in a group of cases such as the 42 per cent in this series that had persistent signs for more than three weeks. (Table III.)

In elderly patients and patients with cardiac disease, rales were incorrectly attributed to causes other than primary atypical pneumonia. For example, a seventy-four year old female was thought to have hypostatic pneumonia until a rise of cold hemagglutinin titer was demonstrated. The nature of the illnesses in Cases I and III was not clear until the suspicion of atypical pneumonia was confirmed by serologic changes. Cases I and II illustrated the alteration of physical signs produced by the adverse effect of atypical pneumonia on the cardiovascular system. Auricular fibrillation and congestive failure occurred in a patient (Case I) with previously compensated rheumatic heart disease. Circulatory collapse with hypotension, tachycardia and pulmonary edema occurred in a patient (Case II) with no previous symptoms or signs of heart disease. Electrocardigrams showed no specific evidence of myocarditis but a conclusion cannot be reached as to whether the cardiac manifestations in these cases were due to general systemic effect of atypical pneumonia or to an actual myocarditis.[28,29]

In using the leukocyte count to aid in distinguishing between primary atypical pneumonia and bacterial pneumonias, reference must be made to the stage of disease at the time the count was made. Normal or elevated counts were seen at any time during the illness. In general (Table V) the leukocyte count was low or normal during the first week of disease and rose to over 9,000 as the disease progressed.[30–33] Two-thirds of the cases had counts below 9,000 on admission; two-thirds of the cases subsequently developed counts over 9,000. This rise in the leukocyte count has been related to beginning resolution of the pneumonia[20,33] and defervescence of fever.[34] In this series the number of patients with leukocytosis was essentially the same before and after defervescence, only three patients showing a normal count while febrile, followed by a leukocytosis when afebrile.

The evidence indicated that the leukocytosis was not due to secondary bacterial infection.[11,35] The pneumococci isolated were the common carrier types and were isolated no more frequently in patients with leukocytosis. Of the forty patients treated with penicillin or sulfonamides none responded to these agents. Lack of such secondary infection has led some observers[31] to state that primary atypical pneumonia actually antagonizes bacterial pathogens. Rather than being due to secondary bacterial infection, leukocytosis appeared to be

a manifestation of primary atypical pneumonia,[36] and a rise in the leukocyte count most often accompanied spread of the pulmonary infiltration.

In the absence of specific etiologic tests the diagnosis of primary atypical pneumonia depends upon recognition of the clinical syndrome and the appearance of serologic changes. Unless cold hemagglutinins or streptococcal MG agglutinins increase in titer the presence of atypical pneumonia in obscure cases, such as those of cardiac disease, may not be confirmed. This difficulty would be compounded if therapeutic agents altered the development of these agglutinins. In past series the incidence of cold hemagglutinins has varied from 5 to 19 per cent[10,37] to 80 to 93 per cent.[38–43] In hospitalized cases such as reported in this series, approximately 60 per cent of the patients developed rises of cold hemagglutinin titers.[13,44–50]

A rise of streptococcal MG agglutinin titer occurred less frequentiy. Except for a high incidence of 65 per cent in a few series,[10,42,47] other series reported an incidence of about 45 per cent.[13,45,49,51] Comparison of cold hemagglutinin titers[10,30,38–41,43–49,52,53] and streptococcal MG agglutinin titers[10,49,53] indicated that the slower rise of the streptococcal MG agglutinin titer may prove useful in the diagnosis of certain cases seen late in the course of disease.

The apparent correlation of the presence and magnitude of rises of agglutinin titers with such measures of clinical severity as duration of fever and extent of pulmonary infiltration[10,13,30,45,46,48,53] has not been universally observed.[10,38–41,43,50,54,55] A reduction in severity produced by therapeutic agents should be associated with a decrease in the duration of fever and a limitation of the extent of pulmonary infiltration. A study of agglutinin titers in a series such as this would permit further observations as to the real significance of this correlation.

The diagnosis of atypical pneumonia as now defined must rest on the roentgenographic demonstration of pulmonary infiltration. In groups of cases right and left lungs were affected with equal frequency, the lower sectors and then the middle sectors being most commonly involved.[7,56–61] In individual cases lobar consolidation resembled bacterial pneumonia, or unilateral upper lobe lesions were difficult to differentiate from tuberculosis.[8,29,62–71] In this series 57 per cent of the patients had two or more sectors involved. The previously reported incidence of multiple lesions has ranged from 10 to 22 per cent.[7,22,58,60,61] More extensive pulmonary infiltration can be expected in a civilian population since only the more ill patients are hospitalized.[57]

In contrast to milder cases seen early in their disease[22,31,58,63,65,71–75] all but 5 per cent of these cases had abnormal pulmonary signs or roentgenograms on admission. Many reports[7,8,11,13,31,53,56–58,60,61,63,65,71–82] have stressed the occurrence of roentgenographic findings with no or few abnormal pulmonary signs. Few authors[83,84] have disagreed with this observation. One-fourth of the cases in this series showed this phenomenon. However, in 18 per cent of the cases on admission the situation was reversed and signs were present or extensive while the roentgenograms were normal or showed only minimal involvement, an observation rarely mentioned.[56,74]

In the absence of a specific diagnostic test, knowledge of these clinical and laboratory variables is of particular value in recognizing primary atypical pneumonia. It is emphasized that the diagnosis is one of exclusion and that use should be made of such specific procedures as are available to exclude agents known to produce similar syndromes.

SUMMARY

A review of sixty-seven cases of primary atypical pneumonia observed in a general hospital emphasizes the variety of clinical patterns attributable to this disease. The illnesses ranged in severity from an obscure fever to a severe pulmonary infection with circulatory collapse. Not only did this syndrome mimic tuberculosis and other

forms of pneumonia but, particularly in older individuals, it also was confused with cardiac decompensation, emphysema and chronic bronchitis associated with other febrile illnesses.

Equal numbers of patients had onsets resembling a common cold, or tracheobronchitis, or "grippe." The most common symptoms were cough, malaise, fever, sore throat, chilliness, anorexia and headache. The average patient had been sick for ten days before admission and experienced maximum temperature on the eleventh or twelfth day of disease. Seventy-nine per cent of the patients were afebrile by the end of the third week of illness.

On admission 50 per cent of the cases had pulmonary signs which corresponded in extent with the amount of infiltration shown by roentgenograms. The other 50 per cent showed discrepancies between signs and roentgenograms, almost as many patients exhibiting predominance of signs as exhibited predominance of infiltration on roentgenograms. In ten cases the correlation between physical findings and roentgenographic changes remained poor throughout the illness and in most of these cases the signs spread widely while the roentgenographic picture remained unchanged. The average duration of abnormal pulmonary signs after onset was three weeks but 15 per cent of the cases had such signs for more than four weeks.

The level of the leukocyte count on admission was related to the duration of disease. Two-thirds of the patients had counts below 9,000 on admission; two-thirds had counts over 9,000 during hospitalization. An increase in leukocyte count most often accompanied spread of the pulmonary lesion. Counts as high as 35,000 may occur in primary atypical pneumonia in the absence of secondary bacterial infection.

Fourfold or greater rises in titer, either of cold hemagglutinins, of streptococcal MG agglutinins or both, occurred in forty-three cases, 65 per cent, in direct correlation with the severity of the illness as measured by duration of fever and extent of pulmonary involvement.

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Dynamics of Isolated Pulmonary Stenosis*

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The occurrence of isolated pulmonary stenosis is extremely rare. In a recent review Greene et al.[1] were able to collect only sixty-eight cases from the literature of isolated pulmonary stenosis confirmed at autopsy. They added four similar cases of their own, diagnosed by right heart catheterization technics. Dynamic studies of three additional cases of pure pulmonary stenosis have been reported by Pollack.[2] While information regarding the dynamics of this lesion is still scarce, the discrepancy between such data and the commonly accepted clinical picture of the lesion is already evident.

The recently revived interest in valvulotomy and the attempt to use this technic for the repair of stenosed pulmonic valves[3] necessitate a precise preoperative anatomic diagnosis and the exclusion of other possibly associated congenital defects, and in addition requires an accurate estimation of the extent of the dynamic changes present. It is for this reason that we are reporting another case of isolated pulmonary stenosis in which catheterization studies and angiocardiography were done.

CASE REPORT

The patient, an eleven year old white female, was referred for cardiac investigation because of a heart murmur believed to be congenital in origin. At the age of six weeks, following a normal birth, the patient was observed to be "blue" on one occasion. Her mother stated that the patient had transient cyanosis following moderate exertion throughout infancy and childhood. The patient was said to tire easily and to lack a normal capacity for exertion. She was congenitally deaf, as were three of five siblings. There was a past history of repeated episodes of tonsillitis.

Physical examination revealed a normally developed, well nourished girl without cyanosis or clubbing. A marked systolic thrill was felt in the second left interspace. On auscultation, a coarse systolic murmur was heard over the entire precordium and posteriorly at the bases of the lungs. The heart sounds at the apex and the second right intercostal space were normal. The pulmonic second sound was clear and louder than the aortic second sound. The pulse was regular. The blood pressure was 110/70 mm. Hg. Physical examination otherwise was negative. No special studies were attempted to elucidate the lesion responsible for the deafness.

Fluoroscopy revealed a globular heart lying as much to the right as to the left of the sternum. The main pulmonary artery was prominent when viewed in the right anterior oblique position. The pulmonary window was abnormally small; the chambers of the heart were not enlarged. The esophagus was not displaced. No hilar dance was seen. A teleoroentgenogram of the chest in the postero-anterior position was suggestive of slight enlargement of the right auricle. (Fig. 1.)

The electrocardiogram (Fig. 2) showed slurring and notching of the QRS complexes in each of the standard and aV limb leads, especially in aVL and aVF. S-T was slightly depressed in leads I and II and elevated in aVR. The T wave was inverted in lead I and aVL. In the chest leads the voltages were large in and to the right of the transition zone. V_5–V_7 showed low voltage with a low T in V_6 and diphasic T in V_7. The contour of the record suggested delay in activation of the left ventricle in conjunction with other non-specific abnormalities. The possibility of an atypical heart strain pattern could not be excluded. Further studies by all other methods failed to reveal any evidence of left heart strain.

Right heart catheterization was performed

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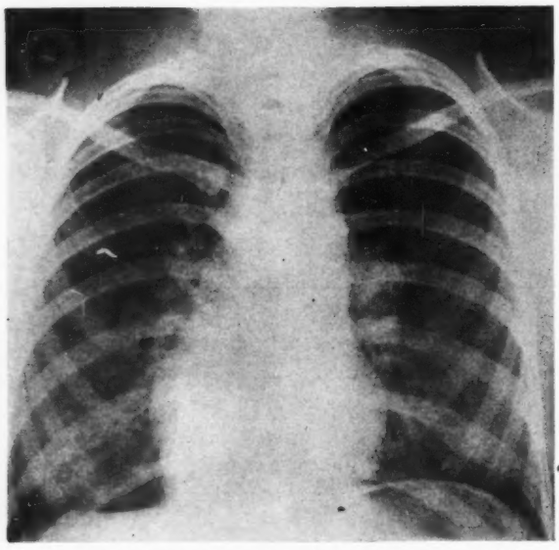


FIG. 1. Roentgenogram in postero-anterior position; note globular heart with prominence to right of sternum. Both pulmonary arteries, particularly the left, appear abnormally dilated.

and the results are summarized in Table I. The constancy of oxygen content in blood samples from different sites indicated that no left to right shunt was present. The complete saturation of the arterial blood excludes the presence of an interauricular septal defect with a right to left

TABLE I
CARDIAC CATHETERIZATION DATA

Location of the Catheter	Oxygen Content (vol. %)	Pressure	
		Systolic (mm. Hg)	Diastolic (mm. Hg)
Superior vena cava	12.2	...	..
Right auricle	13.0	...	..
Right ventricle	13.0	65	5*
	13.7		
Main pulmonary artery	13.0	30	18
Left pulmonary artery	13.0	30	18
	13.9		
Femoral artery	17.1 (99%)	110	70

Cardiac output: 4.9 L./minute.
* End diastolic

shunt. The pressure tracings from the right ventricle and pulmonary artery taken at the point of its branches are shown in Figure 3. The systolic pressure in the right ventricle was markedly elevated (65 mm. Hg) and the pressure gradient between the right ventricle and

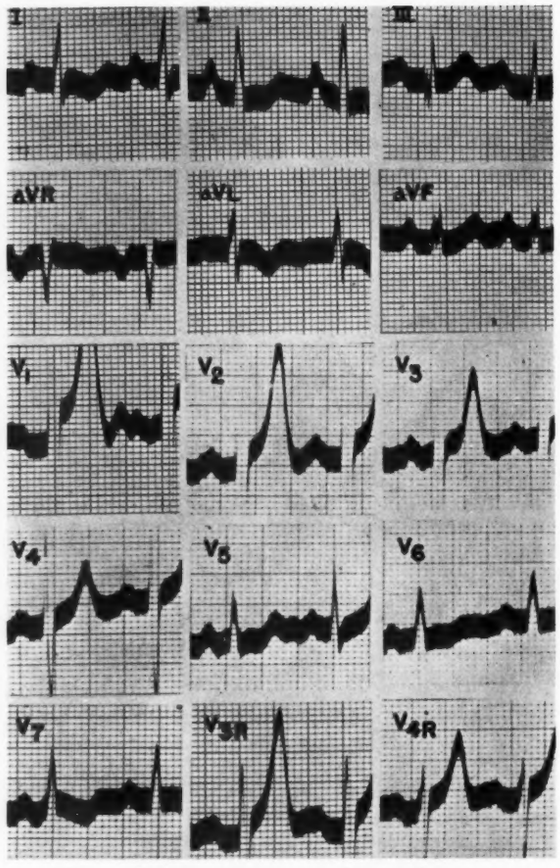
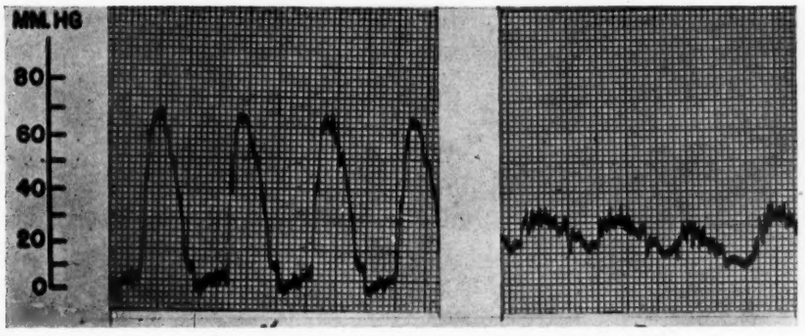


FIG. 2. Electrocardiogram; discussed in text.

pulmonary artery was 35 mm. Hg. On the basis of this pressure gradient the diagnosis of pulmonary artery stenosis was made. Despite this, the diastolic pressure in the pulmonary artery was high (18 mm. Hg).

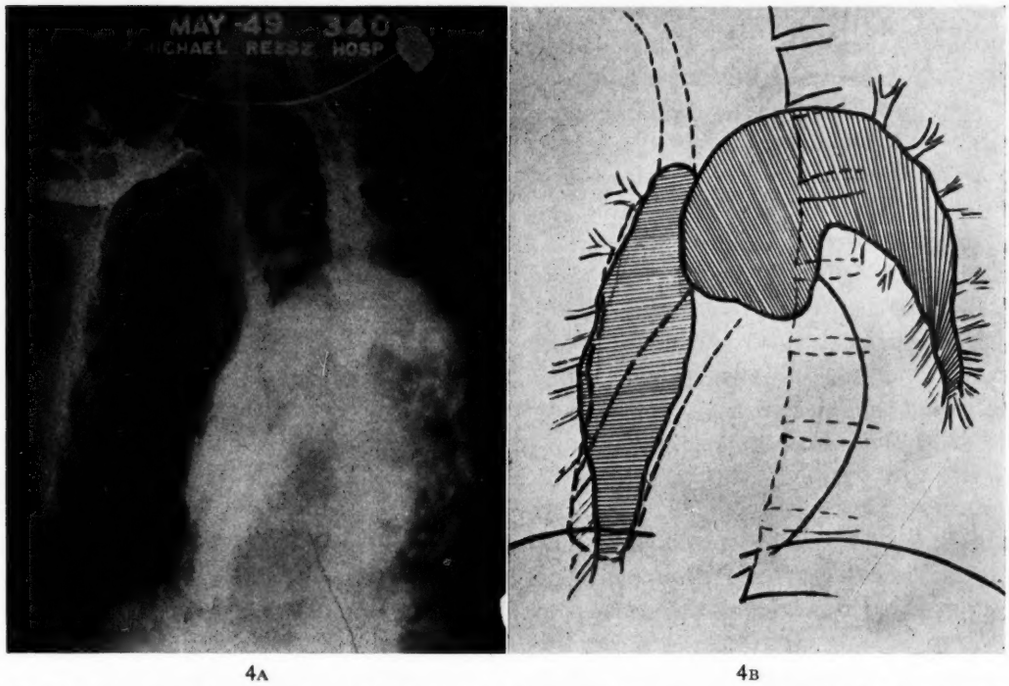
Angiocardiography was utilized in order to visualize the stenotic area and pulmonary arterial tree. Good films of the superior vena cava, right heart and pulmonary arteries were obtained in the left anterior oblique view. (Fig. 4.) These revealed a right-sided superior vena cava, a normal sized right atrium and a normal bulge of the interventricular septum into the cavity of the right ventricle. The infundibular portion of the right ventricle was approximately 1.5 cm. in diameter; stenosis could not be identified with certainty from these films. The main pulmonary artery was large, measuring 4 cm. in diameter. The left pulmonary artery was also dilated. The small branches of the pulmonary artery were sparse.

The final diagnosis was infundibular stenosis with dilatation of the pulmonary arteries and its branches and marked right ventricular and pulmonary hypertension.



3A 3B

FIG. 3. Pressure tracings from (A) right ventricle and (B) main pulmonary artery.



4A 4B

FIG. 4. A, angiocardiogram taken in left anterior oblique position about two seconds after injection of 45 cc. of diodrast. Note the prominently dilated left pulmonary artery with conspicuous absence of medium-sized branches. B, diagram of dye-filled chambers seen on left. The right pulmonary artery was sketched in by superimposing a later film of the series in which this vessel was clearly visualized.

COMMENT

The development of intracardiac catheterization has made possible the employment of physiologic criteria for the diagnosis of pulmonary stenosis. These criteria are: (1) an elevated systolic pressure in the right ventricle and (2) a marked disparity between the systolic pressures of the right ventricle and pulmonary artery. They are applicable to both pulmonary stenosis occurring as part of complicated malformations, such as tetralogy of Fallot, and to the isolated condition. When multiple anomalies are present, the increase in right ventricular pressure may be altered by the presence of shunts or other defects, for example, by tricuspid stenosis. The pressure difference between the right ventricle and pulmonary artery, on the other hand, is an invariant and is pathognomonic of pulmonary stenosis. This difference between the systolic pressures can be considered an index of the degree of stenosis present and is dependent upon (1) the cross sectional area of the stenosed outlet channel, (2) the length of the stenotic area and (3) the volume of blood

ejected from the right ventricle (i.e., the cardiac output). A simple relationship, namely,

$$\frac{\text{pressure gradient (mm. Hg)}}{\text{cardiac output (L.)}}$$

might be obtained as an approximate numerical expression of these functions. Such a *Stenotic index* could be used to quantitate roughly, for comparative purposes, the dynamic significance of the stenosis. It would vary directly with the length and inversely with the cross sectional area (in a non-linear fashion). The value of the index in our case, by such calculations, is 7; it is 15 in one of Greene's cases and 33 in one of Pollack's.

From an anatomic standpoint pulmonary stenosis may be differentiated into a valvular and subvalvular or infundibular type. This distinction cannot be made with certainty by cardiac catheterization. However, angiocardiography, if successful, does help in the differentiation,[4] but good visualization of the outflow tract of the right ventricle and the area of the pulmonary conus and main pulmonary artery is not a simple matter. There is general agreement that the clinical differentiation of these two anatomic types can perhaps best be made by means of the character of the pulmonic second sound. A loud clear sound favors the subvalvular variety of stenosis. Only seventeen of the sixty-eight cases collected by Greene[1] were of this type.

The cause of infundibular pulmonary stenosis is attributed to arrest of incorporation of the bulbus cordis into the right ventricle. It is not easy to account for the dilatation of the pulmonary artery which occurs in about half of the cases. According to Cavina,[6] who studied experimentally produced stenosis, this dilatation of the pulmonary artery is the result of turbulent flow which inevitably follows creation of marked narrowing of the vessel. From a study of our case this mechanism is not adequate to account completely for the pulmonary dilatation. The angiocardiograms demonstrated dilatation of the pulmonary arterial tree extending far into the periphery in both branches. The branches were saccular and showed less peripheral branching than was to be expected. Furthermore, pulmonary diastolic hypertension was present. The pulmonary diastolic pressure depends on the rate of drainage of blood in diastole and is, therefore, primarily a function of the resistance of smaller branches of the pulmonary arteries (pulmonary peripheral resistance). From a dynamic standpoint there is no reason to expect that the presence of pulmonary stenosis should influence the peripheral diastolic drainage, particularly since it has been shown that the pulmonary flow under normal conditions may increase substantially without any changes in pulmonary arterial pressure.[6] It would, therefore, appear that in our case the dilatation of the pulmonary artery and probably the other anomalies in its smaller branches are caused by maldevelopment of the whole pulmonary vascular tree. That this may be the cause in whole or in part of the pulmonary artery changes observed in other cases is suggested by the existence of a pulmonary diastolic pressure above 10 mm. Hg in two of three cases reported by Pollack and in three of four cases reported by Greene. In Greene's remaining case the pulmonary pressure rose on exercise from 15/4 to 32/19.

Re-examination of the clinical picture associated with this anomaly seems warranted in view of newer knowledge elucidated by cardiac catheterization during the past two years. The generally accepted concept that the outstanding clinical features of isolated pulmonic stenosis are dyspnea and cyanosis of varying degree is based upon the belief that only a small amount of blood is pumped into the pulmonary circuit.[7] That this is fallacious, at least in patients who survive the first two years of life, is already apparent from the limited physiologic data available. The cardiac output in our case was 4.9 L./minute. It was 4.5 L./minute in the one case of Pollack's in which data on this point were reported and 4.8 L./minute in one of Greene's cases. The

cardiac indices of the remaining three cases of Greene's were 2.76, 5.42 and 3.70. In one of Greene's cases the cardiac index rose to 12.2 on exercise. Furthermore, a child reported by Freed[8] had a sufficient cardiac output to enable it to live eleven months with a stenosis which left an opening of only 2 mm. in diameter. Further evidence pointing to an adequate cardiac output is indicated by the arterio-venous (A-V) oxygen difference. The A-V oxygen differences were less than 5 volumes per cent in our case and in all reported cases with the exception of one of Pollack's cases. In the latter the possibility of associated rheumatic carditis existed. It appears, therefore, that the cardiac output is not ordinarily decreased by pulmonary stenosis.

A normal cardiac output is maintained in isolated pulmonary stenosis by virtue of an abnormally high energy expenditure by the right ventricle, leading to the establishment of abnormally high right ventricular pressures in the presence of a normal cardiac output. This increased strain on the right ventricle ultimately leads to right heart failure if intercurrent diseases do not intervene to cause the exitus of the patient. It is at this point that dyspnea makes its appearance. In the majority of the reports in the literature, the patients came under observation when in congestive failure making the data concerning dyspnea (and cyanosis) difficult to evaluate. The dyspnea of our case was attributed to an effort syndrome resulting from a life of restrained activity imposed by the child's deafness. No dyspnea was present in Greene's patients. It appeared shortly before the onset of a febrile illness (possibly subacute bacterial endocarditis) in the first of Pollack's cases. Dyspnea had been present in his second patient, only on exercise, such as rapid stair climbing, and was not mentioned in this third case.

Also deserving closer scrutiny are the generally accepted statements about cyanosis in isolated pulmonary stenosis. In the absence of a right to left shunt cyanosis in these cases should develop only when the right heart temporarily or ultimately fails leading to peripheral stasis. This may occur transiently during exercise when the right ventricle is unable to increase its output sufficiently. One case of Greene's was able to increase the cardiac output by 300 per cent under effort. There was no cyanosis in Greene's case. There is a history of a cyanotic spell at the age of six weeks in our case, with mild cyanosis on exertion subsequently, a circumstance which we were unable to reproduce. There was a history of cyanotic spells only during the first seven days of life in one of Pollack's patients. Further observation is needed in these cases to evaluate properly the occurrence of this sign before attributing it to the isolated pulmonary stenosis.

SUMMARY

1. A case of isolated pulmonary stenosis is presented with data obtained by right heart catheterization and angiocardiography. The data are in close agreement with physiologic studies on seven previous cases in the literature.

2. The results of these studies are discussed. It is concluded that patients with pulmonary stenosis are able to maintain an adequate cardiac output at rest and with ordinary activity. The simple relationship, $\frac{\text{pressure gradient (mm. Hg)}}{\text{cardiac output (L.)}}$ = stenotic index, can be considered an approximate numerical expression of the dynamic significance of the pulmonary stenosis.

3. The dilatation of and the high diastolic pressure in pulmonary arteries in the majority of these cases catheterized is associated with intrinsic changes of the pulmonary artery which can be recognized by angiocardiography. It is suggested that the diastolic hypertension, at least in our case and probably in others, is caused by maldevelopment of the whole pulmonary arterial tree, consisting particularly of a decrease in the total number of medium sized and smaller branches of the pulmonary arteries.

4. The generally accepted statement that dyspnea and cyanosis are common findings in pure isolated pulmonary stenosis cannot

be supported by the physiologic data. It is suggested that these changes occur only during temporary or ultimate heart failure and that relative inadequacy of the circulation during stress manifests itself by less dramatic symptoms such as easy fatigability.

Acknowledgment: We are indebted to the other members of the department who assisted in obtaining the data on this patient and to Dr. Stanley Gibson for kindly permitting us to report this case.

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Chronic Cor Pulmonale in Long-standing Bronchial Asthma*

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CHRONIC cor pulmonale is more common than most statistical studies indicate. Inasmuch as it occurs at an age when both coronary arteriosclerosis and hypertension appear, it is frequently unrecognized clinically despite the presence of congestive failure. In a series of sixty cases of chronic cor pulmonale studied at necropsy by Spain and Handler[1] at Bellevue Hospital in 1946 the correct diagnosis was made before death in twenty-four instances, an average of only 40 per cent. Long-standing bronchial asthma almost inevitably leads to emphysema and this, after a long period of time, results in the production of increased pulmonary tension, the forerunner of cor pulmonale. Thus the effects of bronchial asthma on the heart actually become the effects of emphysema on the heart. Recent pathologic studies have clearly demonstrated that emphysema is a frequent cause of hypertrophy and dilatation of the right ventricle. The following four cases of long-standing bronchial asthma with cor pulmonale are presented to emphasize the salient diagnostic features of this entity that may lead to its early recognition.

CASE REPORTS

CASE I. G. M., a fifty year old white male, was admitted to Bellevue Hospital on September 27, 1948, complaining of dyspnea, cough, expectoration, marked weakness and edema of the ankles. His past history revealed that he suffered from bronchial asthma for twenty years. His attacks were paroxysmal in nature and relieved by the injection of adrenalin. In the previous month the dyspnea and cough had become more pronounced and edema of the ankles developed.

Physical examination revealed a fairly well developed adult white male with considerable dyspnea, orthopnea, cyanosis and mental confusion. His temperature was 99°F., pulse 100 and respiration 30 per minute. His hair was gray and had been so for many years. His pupils were equal and regular and reacted to light and accommodation. His fundi revealed congestion of the veins. The chest was barrel-shaped with limited motion of the diaphragms. There was marked hyper-resonance to percussion. On auscultation numerous rhonchi, wheezing and sonorous rales were heard. The heart sounds were distant and no murmurs were audible. The rhythm was regular and P_2 was accentuated. The blood pressure was 108/74. The liver was enlarged three fingers below the costal margin and tender. The lower extremities disclosed two plus pitting edema but no calf tenderness. Clubbing and cyanosis of the fingers and toes were marked.

Urinalysis was completely normal. There were 7,800,000 red blood cells and the hemoglobin was 16.5 gm. The white count and differential were normal. The venous pressure was 220 mm. of water and the ether circulation time was 14 seconds. Roentgen examination of the chest revealed fibroid changes with marked emphysema of both lungs. The right border of the heart was enlarged and the pulmonary artery was prominent. (Fig. 1A.) The electrocardiogram was typical of right ventricular hypertrophy. (Fig. 1B.)

He was treated with the usual cardiac regimen consisting of bed rest, salt free diet, diuretics, oxygen and digitalis. He responded well in a period of two weeks and was discharged to the clinic for follow-up.

CASE II. M. S., a fifty-five year old male, was

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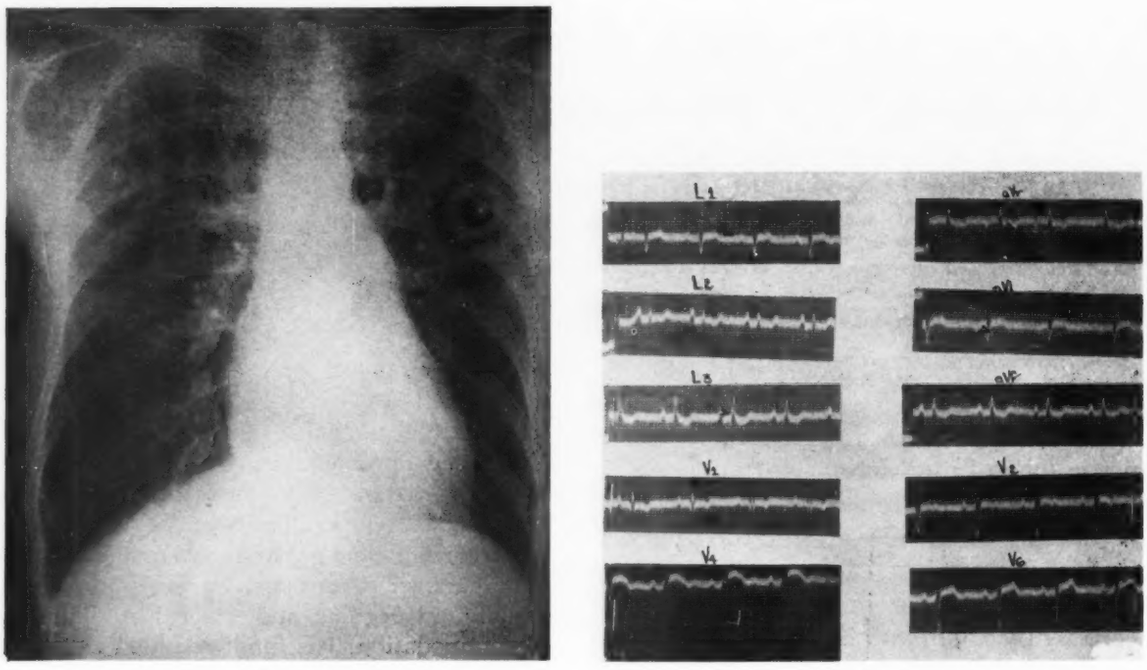


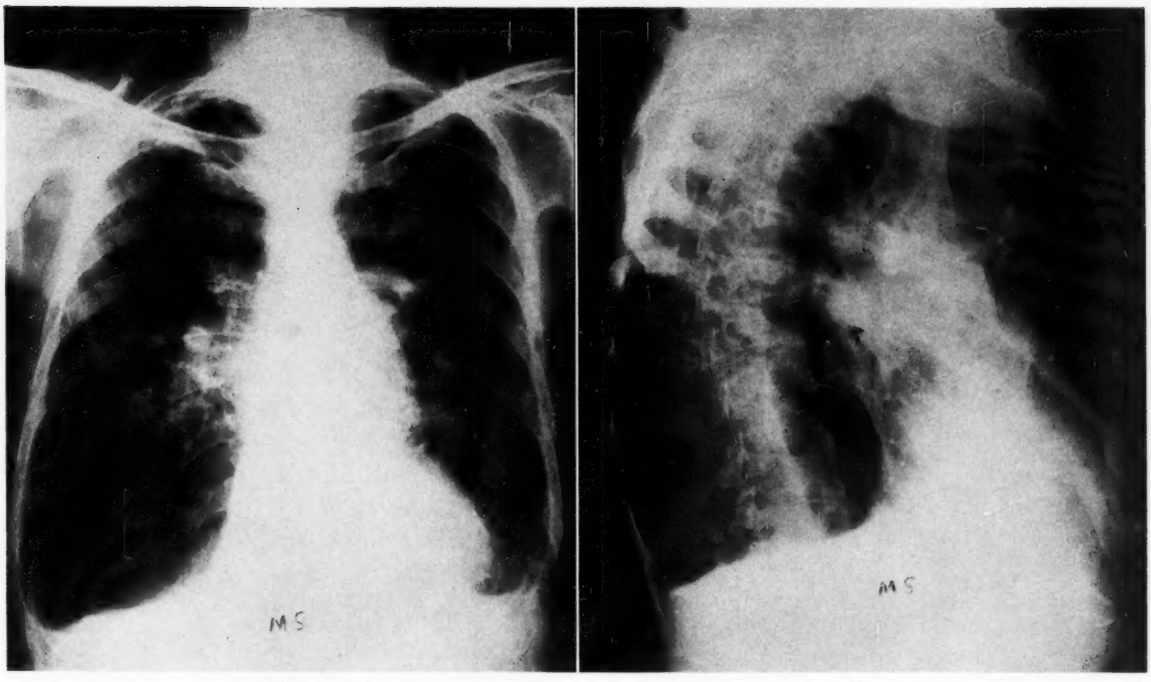
1A 1B

FIG. 1. A, postero-anterior view of Case I (G. M.) indicating fibrosis and emphysema of the lungs and enlargement of the middle left cardiac segment (pulmonary artery). B, right axis deviation of the limb leads and P pulmonale pattern in leads II and III . V_1 shows a qR with an inverted T wave. V_2, V_4 and V_6 show an rS pattern with an inverse R/S ratio over the left precordium. V_R shows a small q, tall R and inverted T. V_L presents a QS and V_F and an RS with diphasic T.

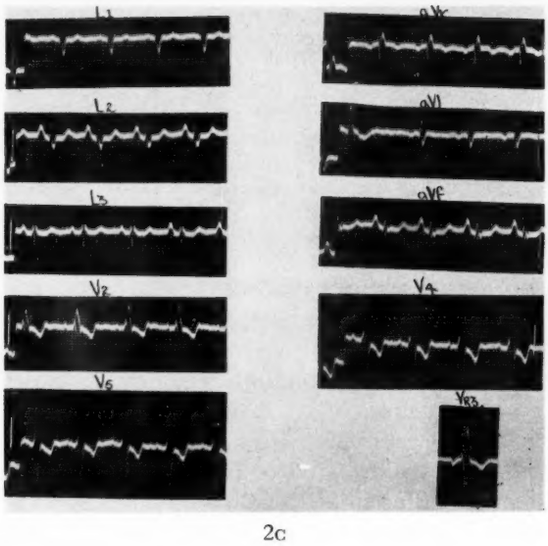
admitted to Bellevue Hospital on July 23, 1947, complaining of severe cough, dyspnea, orthopnea, pain in the right upper quadrant and ankle edema. His past history disclosed that he had suffered from bronchial asthma for twenty-five years. He attended the Allergy Clinic of Bellevue Hospital for the past eight years where he was found sensitive to dust, timothy, ragweed and many foods. During the summer and following infections his attacks became aggravated. He was admitted many times before for severe status asthmaticus and during these episodes of hospital stay a duodenal ulcer and non-functioning gallbladder were discovered. In 1946, while on the ward, an enlarged liver and electrocardiographic evidence of cor pulmonale were detected. His present illness began several days before this admission with increased cough, dyspnea, pain in the right upper quadrant and edema of the ankles.

Physical examination revealed a poorly developed and poorly nourished adult white male in acute respiratory distress. Cyanosis, dyspnea and orthopnea were marked. His pupils were equal and regular and reacted to light and accommodation. The fundi revealed congestion of the veins but no hemorrhages or exudates. The neck veins were distended. There was a marked increase in the anterior posterior diameter of the chest with widening of the intercostal spaces and fixation of the diaphragms. There was hyper-resonance to percussion and on auscultation many rhonchi, wheezes and subcrepitant rales were heard. The heart sounds were distant and feeble and the rhythm was regular. There were no murmurs audible and the P_2 was accentuated. The blood pressure was 110/78. The liver was enlarged three fingers below the costal margin and no other organ edges or masses were palpable. The lower extremities revealed two plus edema and cyanosis of the toes and fingers was evident. There was no clubbing. The reflexes were normal and there was no lymphadenopathy.

The urinalysis and blood chemistry were normal. There were 5,500,000 red cells with a hemoglobin of 15.5 gm. The white blood cells were 9,200 per cc. with a normal differential. The venous pressure was 210 mm. of water with slight elevation of the ether circulation time. His temperature was 99.8°F., pulse 100 and respiration 30 per minute. The x-ray revealed marked emphysema and fibrosis of the lungs with marked enlargement of the pulmonary



2A 2B



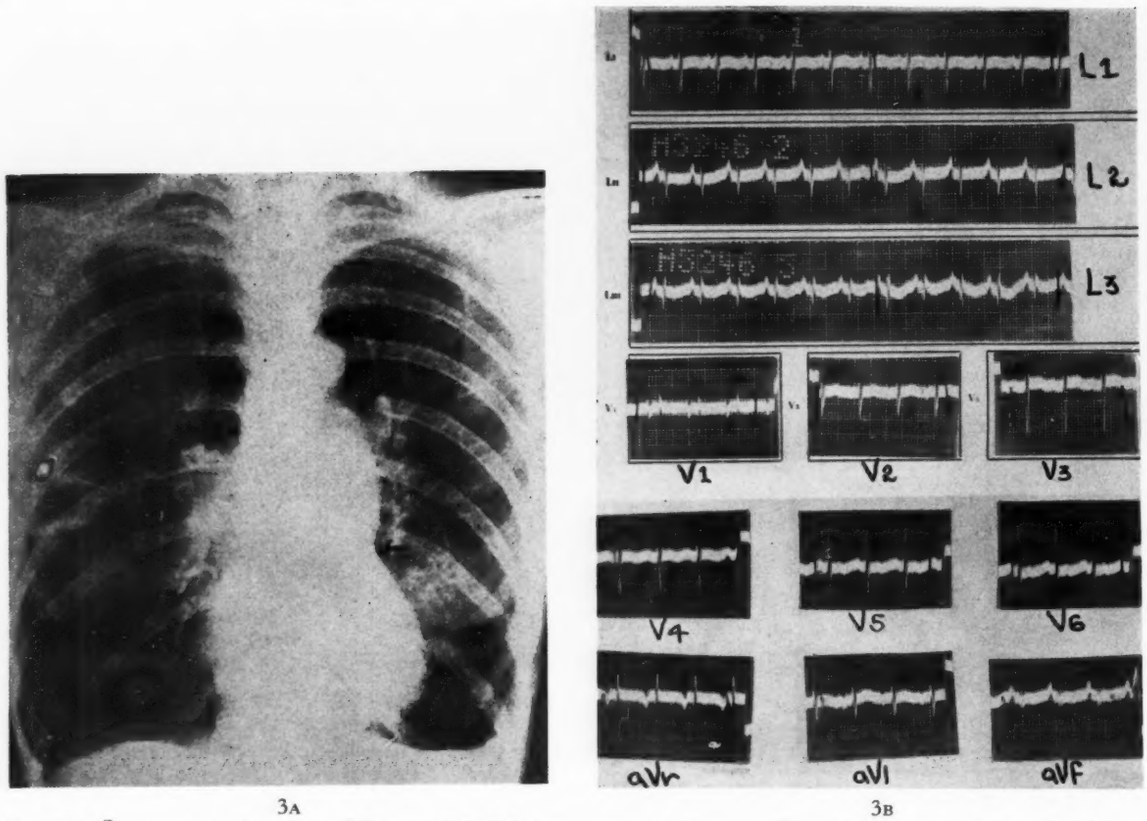
2C

FIG. 2. A, postero-anterior view of Case II (M. S.) indicating marked emphysema with low fixed diaphragm, enlargement of the main pulmonary artery and its right branch. B, right oblique view illustrating enlargement of the right pulmonary artery between the arrows. C, standard limb leads reveal incomplete right bundle branch block with tall P_2-P_3 waves. The unipolar precordial leads show a RR′ with inverted T and a delay in the onset of the peak of R′ and a broad S from the left side of the precordium. V_{3R} is similar to V_1.

artery. (Figs. 2A and B.) The electrocardiogram demonstrated complete right bundle branch block with a P pulmonale pattern in the limb leads. (Fig. 2C.)

With complete bed rest, digitalis, salt free diet, diuretics and oxygen, his congestive failure improved. Oxygen was employed cautiously because of an early paradoxical reaction to it. After four weeks he was discharged to the Cardiac and Allergy Clinics. Since then he has returned to the hospital several times in right-sided failure.

CASE III. M. D., a sixty-two year old white female, was admitted to Bellevue Hospital on February 20, 1948, complaining of cough, dyspnea and swelling of the ankles of two weeks' duration. For the past twenty years she had had periodic attacks of bronchial asthma that were relieved by asthma powders and adrenalin. She attended various allergy clinics and was told that she was sensitive to dust for which she was treated. Her attacks were worse in the winter months. About one and a half years prior to admission she noticed an increase in dyspnea



3A 3B

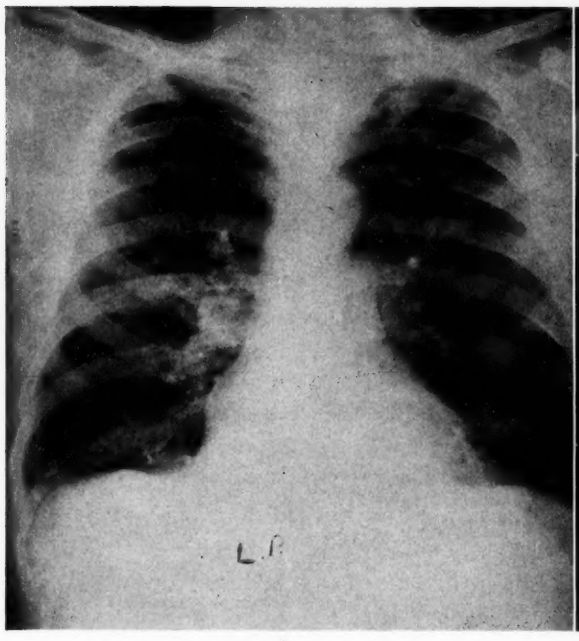
FIG. 3. A, postero-anterior view of Case III (M. D.) demonstrates pulmonary fibrosis and emphysema and enlargement of the pulmonary artery (between arrows). B, right axis deviation and P pulmonale pattern apparent in standard limb leads. There is a small q and tall R in V_1 with an isoelectric T and a persistence of the RS pattern over the rest of the precordium. The unipolar limb leads display a qR in V_R and evidence of a vertical heart in VL and V_F.

and cough. She was then digitalized and held on a maintenance dose.

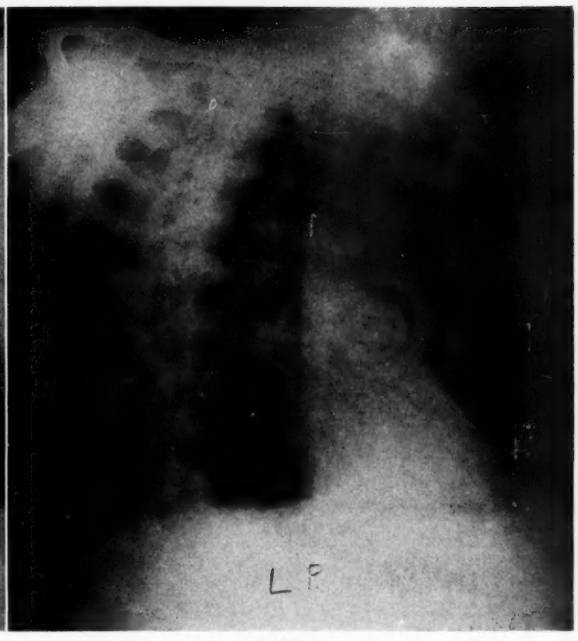
Physical examination revealed a fairly well developed and well nourished adult white female with marked cyanosis, dyspnea and orthopnea. Her hair was gray and had been so for many years. The temperature was 99.2°F., pulse 120; respiration rate 30 per minute. The neck veins were distended. The chest was symmetrical with marked increase in the anterio-posterior diameter. The intercostal spaces were widened and the diaphragm showed little movement. There was hyper-resonance to percussion and numerous rhonchi, wheezing and coarse rales were heard. The heart sounds were distant and no murmurs were detected. The P_2 was accentuated and the rhythm was regular. The blood pressure was 154/84. The liver was three fingers below the costal margin but no other masses or viscera were palpable. The finger nails were cyanotic and there was clubbing of the toes and fingers. There was three plus edema of the ankles but no calf tenderness. The reflexes were physiologic and there was no lymphadenopathy.

Urinalysis revealed a specific gravity of 1.016 with two plus albumin and no sugar. There were no casts or cellular elements on microscopic examination. The blood count was 6,380,000 red cells with a hemoglobin of 16.0 gm. The white blood count was 11,800 with a normal differential. The blood chemistry was normal and serologic tests for syphilis were negative. The sputum was negative for tubercle bacilli. The venous pressure was 140 mm. of water and the decholin circulation time was 14 seconds. X-ray taken on January 26, 1948, disclosed enlargement of the heart and pulmonary artery with fibrosis and emphysema of both lungs. (Fig. 3A.) The electrocardiogram revealed right axis deviation in the limb leads and a tall R wave in V_1 and aVr suggesting right ventricular hypertrophy. (Fig. 3B.)

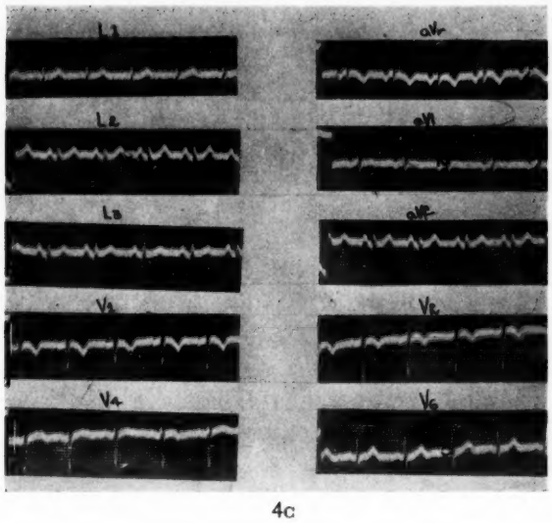
She was treated with bed rest, salt free diet, digitalis, mercuhydrin and aminophyllin with marked improvement. On the twenty-eighth



4A



4B



4C

FIG. 4. A, postero-anterior view of Case IV (L. P.) presents fibrosis and emphysema of both lungs with enlargement of the transverse diameter of the heart and pulmonary artery. B, the right oblique view with enlarged right pulmonary artery between arrows. C, right axis deviation and P pulmonale pattern in standard limb leads. V_1 and V_2 show inverted T waves. There is a persistence of the RS pattern to V_4. The unipolar limb leads indicate a vertical heart.

hospital day she was discharged and referred to the clinic for follow-up.

CASE IV. L. P., a forty-seven year old adult male, was admitted to Bellevue Hospital on October 7, 1948, complaining of severe cough, dyspnea, weakness and edema of the legs. There was no family history of allergy. His past history revealed that he had been suffering from bronchial asthma for five years. These paroxysms of asthma began to develop one year following his occupation as a baker. In the past four months he noted aggravation of his dyspnea and cough and development of ankle edema.

Physical examination revealed a well developed and well nourished adult white male in acute respiratory distress with marked dyspnea, orthopnea and cyanosis. His hair was gray and had been so for many years. His pupils were equal and regular and reacted to light and accommodation. The fundi revealed marked venous engorgement but no hemorrhages or exudates. His chest was barrel-shaped and symmetrical. The intercostal spaces were widened and the diaphragm did not move freely. The respirations were shallow and rapid. There was hyper-resonance to percussion and numerous rhonchi, wheezing and sonorous rales were heard throughout the chest. The heart sounds

were distant and no murmurs were audible. The P_2 was markedly accentuated. The rhythm was regular and the blood pressure was 124/78. The liver was enlarged two fingers below the costal margin and no other organ edges were felt. The lower extremities revealed two plus edema but no evidences of inflammation. Cyanosis and clubbing of the toes and fingers were apparent. The reflexes were normal.

TABLE I

CARDIAC CATHETERIZATION STUDIES

Estimated plasma volume		2,610 cc.
Estimated blood volume		4,745 cc.
Actual plasma volume		2,600 cc.
Actual blood volume		5,950 cc.
Hematocrit		56.3%
Arterial O_2 capacity	20 vol. %	
Arterial O_2 saturation	83%	
Arterial O_2 content	16.5 vol. %	
Arterial CO_2 content	55.6 vol. %	
Mixed venous blood O_2 content	12.2 vol. %	
Mixed venous blood CO_2 content	59.9 vol. %	
O_2 Consumption (N–130)	154 cc./min./M_2 body surface	
(I–130)		
Cardiac output	5.84 L./min.	
Cardiac index (N–3.14 plus .4)	3.58 L./min./M_2 body surface	

$_pCO_2$ = 49–55 (N. 39)

Alveolar—arterial oxygen gradient .. 29–38

Pulmonary artery pressure ..... 34/17 (N—25/8)

Right ventricle pressure—33/0 (N. 30/0)

Results:

1. Increased blood volume with increased cell volume
2. Increased lesser circulation tension
3. Ventilatory deficiency

Urinalysis and blood chemistry were normal. The blood count disclosed a red cell count of 7,700,000 with a hemoglobin of 16.5 gm. The white count was 5,500 with a normal differential. The sedimentation rate was normal and the venous pressure was 98 mm. of water. The sputum was negative for tubercle bacilli. X-ray of the chest revealed enlargement of the heart in the transverse diameter and enlargement of the pulmonary artery with marked emphysema of both lungs. (Figs. 4A and B.) The electrocardiogram revealed right axis deviation and P pulmonale pattern in the limb leads. The precordial leads demonstrated an RS pattern from V_1 to V_4 with inverted T waves in V_1 and V_2. This is compatible with right ventricular hypertrophy. (Fig. 4C.) Cardiac catheterization studies performed by the cardiopulmonary laboratory group at Bellevue Hospital indicated increased pressure in the pulmonary circuit. The results appear in Table I.

He was treated with mercuhydrin, salt free diet, digitalis and oxygen with considerable improvement and was discharged on the thirty-second hospital day to the clinic for follow-up.

COMMENT

All four patients presented a classical history of paroxysmal seizures of asthmatic symptoms with relief by sympathomimetic drugs. Two of these attended the Allergy Clinic at Bellevue Hospital where many positive skin tests were elicited. One had an associated allergic disease (hay fever) and another a clear-cut history of the development of asthma one year following his occupation as a baker. The duration of the asthma was from five to twenty-five years. The pulmonary signs, laboratory evidence and x-ray appearance of the chest in all instances indicated a diagnosis of emphysema. There were three males and one female with an average age of over fifty years. Although no definite statistical conclusions can be inferred from a small series such as this, the data seem to be in accord with what is generally observed in this type of heart disease.

The causes of pulmonary hypertension with inevitable right ventricular hypertrophy can be classified into two main groups, namely, a cardiac and a pulmonary group. The cardiac group consists of left-sided failure due to hypertension, coronary sclerosis and mitral valvular disease with stenosis; congenital defects and aortic aneurysm with pressure on the pulmonary artery. The pulmonary group consists of changes in the lung parenchyma, pulmonary blood vessels and the thoracic cage. Enlargement of the right ventricle resulting from these latter causes is truly termed pulmonary heart disease or cor pulmonale Spain and Handler[1] have tabulated the etiology of cor pulmonale in a convenient manner. (Table II.)

The mechanism whereby emphysema produces hypertrophy of the myocardium of the right ventricle with or without subsequent failure is by no means a settled question. Numerous theories have been proposed

by many observers, among which have been pulmonary vascular sclerosis, diffuse fibrosis of the lungs, obliteration of the pulmonary vascular bed, vascular shunts existing between the systemic and pulmonary circulation, overfilling of the heart, polycythemia and compression of the capillaries by the increased intra-alveolar pressure occurring during the respiratory cycle. Although none of these has been proven, and despite the difference of opinion, there is considerable evidence to indicate that an increased resistance to the flow of blood through the lungs does exist in advanced emphysema. This, over a long period of time, exerts a strain on the right side of the heart with ultimate hypertrophy. The question frequently raised, that if the above is true why do not all cases of emphysema with or without bronchial asthma develop cor pulmonale, still awaits an answer. It is possible that occupational, constitutional, endocrine and neurogenic factors may play an additional part in its etiology.

TABLE II

I. Anatomic Alterations of the Thoracic Cage
   - A. Kyphoscoliosis
   - B. Thoracoplasty

II. Anatomic Alterations of the Pulmonary Vascular System
   - A. Main pulmonary arteries
     1. Intrinsic disease of the large pulmonary arteries, such as gummatous or cicatricial pulmonary arteritis
     2. Pressure on the large pulmonary vessels such as aneurysm arising from the base of the aorta
   - B. Pulmonary arterioles
     1. Primary pulmonary arteriosclerosis: endarteritis obliterans (Ayerza's disease)
     2. Schistosomiasis of the pulmonary vessels

III. Anatomic Alterations of the Pulmonary Parenchyma
   - A. Primary pulmonary emphysema with or without fibrosis
   - B. Primary pulmonary disease with secondary emphysema and fibrosis
     1. Pulmonary tuberculosis
     2. Pneumoconiosis
        - (a) Chronic silicosis
        - (b) Anthracosis
     3. Bronchiectasis
     4. Bronchial asthma
     5. Acute interstitial fibrosis
     6. Multiple cysts of the lung

The observation of premature graying of the hair in three out of the four cases presented suggests an endocrine or constitutional diathesis. Levine[2] states that "Early graying of the hair occurs in four main groups of individuals. First, there is a group of perfectly normal people who begin to have gray or even white hair in the twenties and thirties and among these there are a certain number who have a tendency to premature arteriosclerosis. Then there are three diseases with which it is not infrequently associated, i.e., asthma, hyperthyroidism and pernicious anemia."

The medical literature is replete with unmistakable postmortem evidence of enlargement of the right ventricle in cases of bronchial asthma and emphysema. Huber and Koessler,[3] Harkavy,[4] Rackeman,[5] McDonald,[6] Colton and Ziskin,[7] Sprague[8] and others have demonstrated enlargement of the right ventricle at necropsy in fatal cases of bronchial asthma. Kountz, Alexander and Prinzmetal[9] determined the weight of each ventricle in seventeen cases of pulmonary emphysema. They found evidence of hypertrophy of the right ventricle in ten. In 1943 Schiller, Colmes and Davis[10] analyzed a series of fifteen cases of bronchial asthma studied at autopsy. In three patients in whom the bronchial asthma existed for three years or less the heart was normal. But of the remaining twelve, in whom the duration of the asthma was six years or more, four showed thickening of the right ventricle beyond 5 mm. Spain and Handler[1] in 1946 reported pathologic evidence of chronic cor pulmonale in forty cases of uncomplicated emphysema and in six cases of asthma with emphysema.

Clinical reports of right ventricular failure or hypertrophy of the right ventricle without decompensation in bronchial asthma have been scant. Schiller, Colmes and Davis[10] followed the case histories of fifty-four patients with bronchial asthma and found but one instance of cardiac failure simulating cor pulmonale.

The physical signs and symptoms exhibited by the cases described above may be divided into two phases: an early pulmonary

or precardiac phase and a later cardiac phase. The cough, rhonchi, expectoration, dyspnea, cyanosis, polycythemia, clubbing of the fingers, flaring of the ribs and fixation of the diaphragm are characteristic of the first phase, the underlying bronchial asthma and emphysema. The outstanding features of the second phase are the engorged veins, enlarged and tender liver, generalized edema and increased venous pressure. The transition from one phase to the other is most difficult to detect since dyspnea and cyanosis, the early signs of cardiac failure, are also indicative of the underlying pulmonary disease. However, an increase in these findings or the appearance of orthopnea suggests the onset of strain on the right side of the heart. It is well known that patients with emphysema breathe more comfortably lying down whereas those with cardiac dyspnea are relieved by sitting upright.

Regular sinus rhythm and normal blood pressure are the usual occurrence in cor pulmonale. However, occasionally a disturbed rhythm may be present. Accentuation of the second pulmonic sound is a constant feature and this, with the occasional diastolic pulmonic murmur, suggests the existence of increased intrapulmonary tension. Positive proof of such elevation can be obtained by intracardiac catheterization. The average normal pressure reading in the right ventricle and pulmonary artery is 25/4. In patients with chronic pulmonary disease, i.e., asthma with emphysema but without failure, the systolic pressure alone is heightened. When failure sets in, both the systolic and diastolic pressures rise. Case IV demonstrated a significant increase in the systolic pressure and only a slight rise in diastolic pressure, findings which are consistent with the diagnosis of cor pulmonale and slight failure.

Cardiac enlargement demonstrated roentgenographically in all four cases adds another link in the chain of evidence for the diagnosis of cor pulmonale. Other workers have described similar findings in bronchial asthma and emphysema. Parkinson and Hoyle[11] and Rigler and Hallock[12] reported enlargement of the pulmonary artery and the right ventricle in the postero-anterior and oblique views. Sussman, Steinberg and Grishman,[13] employing contrast cardiography, were able to demonstrate dilatation of the pulmonary artery and right ventricle in twenty-four of twenty-eight cases of emphysema. In this group there were eight cases with associated bronchial asthma. Subsequent work by the same authors[14] indicated that the enlargement of the cardiac shadow on the right depends on the existence of right auricular dilatation and that this together with the prominence of the middle left cardiac segment are indirect signs of right ventricular dilatation. This explanation serves to clarify interpretation of the cardiac silhouette in such instances.

Electrocardiographic changes in bronchial asthma and emphysema have been noted by many. Kahn[15] in 1927 was the first to report changes in the electrocardiogram in bronchial asthma. In a series of fifty cases he found ten instances of right axis deviation and of these four also had tall P_2 and P_3 waves. Subsequently Ungar,[16] Colton and Ziskin,[7] Harkavy and Romanoff[17] and others observed many deviations from the normal, consisting of (1) right axis deviation, (2) R-ST depression with inverted T waves in Leads II and III, (3) deep S waves in all standard limb leads and (4) P wave abnormalities. These changes are not specific of right ventricular enlargement for they may occur in normal as well as in vertical hearts with left ventricular hypertrophy.

The introduction of multiple unipolar precordial and extremity leads has added additional information leading to the interpretation of right ventricular hypertrophy. Normally, leads V_1 and V_2 yield QRS complexes of the rS type and leads V_4, V_5 and V_6, from the left side of the precordium, yield complexes consisting of a small q, tall R with or without a small s wave. On the average, the peak of R is about 0.02 second earlier when the pre-

cordial lead is over the right ventricle than when over the left. However, in right ventricular hypertrophy Wilson and his associates[18] and Goldberger[19] have shown that the reverse is true. From the right side of the precordium, V_1 and V_2, the QRS complex is chiefly an R wave, with an occasional antecedent small q wave, and the S wave is either absent or relatively small. The T wave is characteristically inverted. From the left side of the precordium the R wave is small, the S wave prominent and the T wave is upright. The increased amplitude of the R wave and prolongation of the interval from the beginning of the R wave to its peak in V_1, formerly considered indicative of an increased thickness of the right ventricular wall, it is now agreed is a recorded potential of the left ventricle caused by marked clockwise rotation.

An additional precordial lead is the V_{3R} in which the exploring electrode is placed on the right chest at a point corresponding to V_3 position on the left chest. Myers and his group[20] as well as Kossman and his associates[21] employed this electrode station in cases of suspicious hypertrophy not confirmed by the other precordial leads. In such instances it yielded a small q, a tall R and an inverted T wave in contrast to a small r, deep S normally obtained.

Incomplete right bundle branch block in which there is a double peaking of the R wave in V_1 and a relatively broad S wave in V_6 with the duration of the QRS .10 second or less, as well as complete bundle branch block in which the QRS is greater than .11 second, are frequent although by no means pathognomonic patterns of hypertrophy of the right ventricle.

An alteration in the unipolar limb lead V_R in which there is a tall R preceded by a q wave offers additional electrocardiographic evidence for right ventricular enlargement. This indicates backward displacement of the apex, a positional change commonly found in this condition. The electrocardiographic tracings obtained in the above patients demonstrate some of the many patterns indicative of right ventricular hypertrophy, and strengthen the diagnosis of cor pulmonale.

It is evident from the cases presented that chronic cor pulmonale may develop in bronchial asthma of five years' or more duration associated with emphysema. It can and should be diagnosed clinically on the following criteria: (1) the presence of long-standing bronchial asthma and emphysema without any other associated cardiac disease; (2) the development of an increase in the dyspnea and cyanosis already present; (3) the appearance of orthopnea with or without signs of right-sided failure; (4) the presence of increased pressure in the pulmonary circuit either implied or directly measured by intracardiac catheterization; (5) radiographic demonstration of cardiac enlargement and (6) an electrocardiographic pattern of right ventricular hypertrophy.

Proper treatment and prolongation of life in cor pulmonale demands early recognition.

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Syphilitic Cardiovascular Disease Combined with Chronic Endocardial Lesions Usually Attributed to Rheumatic Fever*

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COMBINED syphilitic and rheumatic cardiovascular disease is usually considered uncommon. Over a period of years a number of presumed instances of coexistent "rheumatic" and syphilitic heart disease have been put on record so that this combination of lesions may be more frequent than is generally held. This study was undertaken in an attempt to examine some of the important clinical and pathologic features of this complex of lesions.

About the turn of the century syphilitic aortitis (the existence of which had been suspected for many years) had been accurately described as an important disease entity.[1–5] With the discovery of Treponema pallidum in the aorta by Reuter[6] and others[7,8] the identity of syphilitic aortic disease and aortic valvulitis was established. It is not surprising, therefore, that definite appreciation of the coexistence of syphilitic and rheumatic heart disease was not gained until little more than twenty five years ago.

Huchard[9] in 1899 anticipated the question in his statements that rheumatic endocardial disease may coexist with arteriosclerosis of the great vessels, of which syphilis was then considered to be an important cause. Two years later Le Gendre[10] described the gross lesions in a heart and aorta exhibiting a large syphilitic aneurysm and marked stenosis of the mitral valve.

In 1910 Longcope[11] published his clear descriptions of the pathology and clinical features of syphilis of the aorta and aortic valves. In a series of twenty-one cases of specific aortic disease he described one autopsied heart showing characteristic aortitis and aortic valve disease, and well defined mitral stenosis. He was uncertain as to the relationship of the mitral and syphilitic lesions. Longcope observed two clinical instances of aortic insufficiency showing positive Wassermann reactions in which there was also evidence of mitral disease. He was impressed with the difficulty of establishing an accurate diagnosis in such cases.

Stolkind[12] in 1921 described the case of a man (aged forty-one) whose history indicated a syphilitic infection at twenty and "rheumatic" polyarthritis at twenty-eight. Autopsy revealed syphilitic aortitis and valvulitis, mitral stenosis and chronic pericarditis. The gross observations were not reinforced by microscopic study. In 1924 Von Glahn and Wilshusen[13] reported two instances of syphilitic aortitis and valvulitis complicated by acute rheumatic myocarditis (mesaortitis and Aschoff bodies microscopically).

Cabot[14] in 1926 wrote that the combination of syphilitic and rheumatic cardiac disease was rare indeed. But thereafter such case descriptions appeared in the literature more frequently.[15–27] To the present time we have been able to find forty-seven cases of possible combined syphilitic-rheumatic cardiovascular disease

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described in the literature. In forty-one of these cases histologic study was carried out in an attempt to evaluate carefully the presence of the two abnormalities. Although some of the pathologic descriptions, especially regarding old or healed rheumatic lesions, may be open to question,[26] it appears that the two diseases were coexistent in most of these cases. All of the reports are summarized in Table 1. A number of instances have been reported[11,16,28,29] in which the coexistence of the two diseases was suspected clinically, without death of the patient.

Syphilitic-rheumatic Cardiovascular Disease in Necropsy Series. In surveys of autopsy series involving large numbers of cases syphilis is commonly found.[30] In some studies examples of combined syphilitic-rheumatic heart disease have been encountered. A few figures may be cited briefly.

Herz[31] appears to have been the first to note this combination of lesions in a general study. Reviewing the pathology of 522 patients who had died with syphilis, he found seventeen examples of syphilitic aortitis with or without aortic valvulitis. Of these, six were said to show aortitis complicated

TABLE 1

BRIEF SUMMARY OF FORMAL REPORTS OF CASES OF COMBINED SYPHILITIC-RHEUMATIC CARDIOVASCULAR DISEASE

Author	Year	Cases	Rheumatic Lesions	Syphilitic Lesions
Le Gendre[10]	1901	1*	Mitral stenosis	Aortitis; aneurysm
Longcope[11]	1910	1*	Mitral stenosis	Aortitis; valvulitis
Stolkind[12]	1920	1*	Mitral stenosis; pericarditis	Aortitis; valvulitis
Von Glahn and Wilshusen[13]	1924	2	Myocarditis, acute	Aortitis
Dumas and Brunat[15]	1927	1	Mitral stenosis	Aortitis
Gallavardin and Gravier[16]	1930	3*	Rheumatic aortitis and valvulitis; aortic stenosis and regurgitation; mitral and aortic endocarditis	All aortitis
Cabot[17]	1929–1933	4†	Mitral endocarditis in 2 cases; acute myocarditis in 1 case; endocarditis all valves, mitral stenosis and aortic valvulitis in others	Aortitis; 2 cases with valvulitis
Roubier et al.[18]	1933	2	Aortic stenosis in 1 case; mitral stenosis	Aortitis
Lisa and Chandlee[19]	1934	6	Various, i.e., pancarditis, chronic endocarditis, mural endocarditis	All aortitis
Sager and Sohval[20]	1934	3	All aortic valvulitis, also with mitral endocarditis, myocarditis, subacute bacterial endocarditis, and tricuspid valvulitis	Aortitis and valvulitis
Cossio and Berconsky[21]	1935	1	Mitral stenosis	Aortitis; valvulitis
Rottino[22]	1938	1	Active mitral and tricuspid endocarditis; acute myocarditis	Aortitis; multiple aneurysms peripheral arteries
Bello[23]	1939	1	Mitral stenosis	Pulmonary artery aneurysm
Heidenreich et al.[24]	1938	1	Mitral stenosis	Aortitis; aneurysm
Swanson[25]	1939	4	Rheumatic myocarditis, 2 cases; aortic stenosis, 1 case; rheumatic mitral and/or tricuspid valvulitis	Aortitis; aortitis and valvulitis in 2 cases
Plice and Edinburg[26]	1942	1	Fibrocalcific mitral disease, stenosis; slight aortic stenosis	Aortitis
Lisa et al.[27]	1942	14	Various, i.e., aortic valvulitis in 9 cases; myocardial Aschoff bodies in 11 cases	All aortitis and valvulitis
Total cases	....	47		
Cases with gross and histologic study	....	41		

* Histologic study not included in reports.

† One case (No. 16492) was omitted as vague.

by chronic mitral valve disease; one case exhibited aortitis and accretio cordis (attributed to rheumatic fever). Cowan and Rennie[32] noted rheumatic endocarditis in 3.1 per cent of a group of hearts showing syphilitic infection, and Buday[33] stated that of his cases of syphilitic heart disease 6 per cent showed evidence of chronic rheumatic endocarditis. Wood et al.[34] described three instances of combined infection in a series of fifty-five hearts showing syphilitic disease.

Within the past sixteen years a number of observers[19,20,25,35,36] have reported such coexistent cardiovascular lesions in autopsy series. DeGraff and Lingg[37] studied the pathologic findings in 644 patients who had died of rheumatic heart disease. Among these were six examples of complicating syphilis of the cardiovascular structures. Plice and Edinburg[26] observed 319 postmortem cases of cardiovascular syphilis; there were fifty-three of this number considered to show evidence of rheumatic endocarditis. Lastly, Lisa et al.[27] studied 311 hearts with syphilitic aortitis; rheumatic endocarditis was found in thirty-one (10 per cent) of these specimens.

PATHOLOGIC STUDY

Interest in the combination of syphilitic and rheumatic cardiovascular disease from the clinical and pathologic standpoints was fostered by the study of a case in which the cardiac diagnosis was confusing. This case is presented briefly:

M. F., a forty-five year old white laborer, entered the St. Louis City Hospital on March 15, 1945. The patient had suffered gradually increasing dyspnea for four months; orthopnea had been present for two months. Sleep was frequently broken by paroxysms of breathlessness. Edema of the lower extremities was progressive. There was no past history suggesting rheumatic fever; scarlet fever and attacks of sore throat or tonsillitis were denied. A penile lesion had appeared ten years previously for which the patient stated he had received twenty-four intravenous injections. The identity of the drug could not be ascertained.

Examination showed a poorly nourished, chronically ill man with marked dyspnea, orthopnea and cyanosis of the lips and nailbeds. Significant findings were confined to the cardiovascular system. The cardiac dullness extended 12 cm. to the left of the mid-sternal line (fifth interspace); the apical cardiac impulse was diffuse from the fifth to the seventh interspaces at the left mid-axillary line. The ventricular rhythm was irregular, denoting auricular fibrillation, with an apical rate of 68. There were no thrills. A long, high-pitched early diastolic murmur was detected over the aortic area and along the left sternal border. The first sound was of "poor quality." A rumbling diastolic murmur was heard at the apical region; the murmur was judged to be mid-diastolic and late diastolic in time. In addition a harsh mitral systolic murmur of medium intensity was evident. Blood pressure was 165/40 (lying) in both arms. Numerous coarse rales were noted at the lung bases. There was moderate hepatic enlargement and edema of the lower extremities and sacrum. The blood Kahn test was positive.

Roentgenologic examination (postero-anterior chest film) revealed cardiac enlargement, with distinct widening of the shadow of the ascending aorta. A linear mark of calcium was noted within the silhouette of the aortic knob. The diagnosis of aortitis with a small fusiform aneurysm was suggested. Degenerative changes within the aorta were considered probable on the basis of aortic calcification.

From the clinical findings it was reasoned that the heart disease might either be due to syphilitic aortitis and valvulitis or to chronic rheumatic disease with mitral and aortic deformities. In support of the diagnosis of syphilis was the evidence of aortic dilatation, aortic valvular insufficiency and the history of a penile lesion. The mitral diastolic murmur was considered to be an Austin Flint murmur by a number of examiners. The alternative diagnosis of chronic rheumatic heart disease (with mitral stenosis and aortic insufficiency) likewise seemed tenable. Although there was no history of rheumatic fever earlier in life, the distinctive character of the physical signs suggested rheumatic heart disease. Auricular fibrillation, while occasionally seen in syphilitic heart disease, is a common complication of mitral stenosis and was thought to lend some support to the latter diagnosis. Unfortunately the patient was too ill to undergo fluoroscopic study with respect to left auricular enlargement. These questions

relating to the etiologic diagnosis of the heart disease were extensively discussed during the patient's hospital course and one or the other diagnosis was made by the various examiners. The question of combined syphilitic-rheumatic cardiovascular disease was not mentioned.

The patient subsequently died of congestive heart failure.

Autopsy revealed the following: The general development of the body was normal. The heart was enlarged and weighed 750 gm. Grossly, the ascending aorta appeared to be nearly twice normal width. Gross appearance of the pericardium and epicardium was normal. The endocardium was smooth except at the exit of the aorta where it was definitely thickened. The chorda tendineae were markedly shortened and thickened. Myocardial hypertrophy was noted: thickness of the left ventricular wall, 2 cm.; thickness of the right, 1.4 cm. The coronary arteries and their orifices were patent; these arteries showed a few small raised plaques. The lines of coaptation of all of the aortic valve leaflets were rolled and thickened.

The wall of the ascending aorta was thickened and sclerotic. The intima exhibited many raised gray and grayish blue plaques together with marked longitudinal wrinkling and furrowing. The mesaorta was thickened. On section many small vessels were seen, grossly, in the tunica media. The descending thoracic and abdominal portions of the aorta were not remarkable.

Microscopic examination of the aorta showed intimal thickening and marked vascularization of the media and adventitia with round cell infiltration particularly about the vasa vasorum. Examination of the heart revealed hypertrophy of the muscle fibers which in places were fragmented. There was marked perivascular fibrosis throughout the myocardium. No myocardial Aschoff bodies were seen. The margin of the mitral valve was thick and cellular.

On the basis of gross and microscopic findings the aorta and aortic valve were judged to show the changes characteristic of syphilitic disease. In addition the anatomic diagnosis of chronic endocarditis of the mitral valve (possibly rheumatic in origin) seemed justified. Very little stenosis of the mitral valve was apparent grossly; however, the shortening of the chorda tendineae and resulting inflexibility of the valve leaves were thought to render the orifice functionally narrowed. It is now clear that the two categories of cardiac disease were reflected in physical signs which may have indicated either one of the two diagnoses; since the possibility of combined lesions was not entertained, the actual diagnosis was missed.

Pathologic Material. A search for similar cases was made in the records of the Department of Pathology, Washington University, and the Pathology Division of the St. Louis City Hospital. Autopsy protocols from the years 1930 through 1946 (inclusive) were examined and all cases showing syphilitic cardiovascular disease and acute rheumatic or chronic endocardial lesions of possible rheumatic origin were included in the study. The disease of the heart was not necessarily the major lesion(s). All patients were adults, the minimum age being eighteen years. Autopsies of younger persons having died of (or with) rheumatic heart disease were not included because of the low incidence of acquired syphilis in such a group. The protocols of all cases were scrutinized for descriptions of lesions suggesting both syphilitic and chronic "rheumatic" processes. Microscopic sections from all such cases were at hand.

The pathologic features of syphilitic aortitis and aortic valvulitis are generally distinctive and are well established;[30,38,39] these established criteria were employed in identifying the lesions in the present cases. The identity of "rheumatic" cardiac lesions in the absence of Aschoff nodules is more difficult to prove. In general the chronic endocardial deformities leading to commisural adherence of valve leaflets and retraction of the membranes, and apparent old inflammatory processes producing perivascular fibrosis,[39,40,42,43] together with localized endocardial fibrosis, vascularization and infiltration with myocardial histiocytes[41,44] were interpreted as changes most probably associated with rheumatic fever. A history in a given patient suggesting rheumatic polyarthritis or other symptoms indicative of rheumatic fever was taken into account.

Incidence of Syphilitic Lesions Combined with Chronic "Rheumatic" Lesions in Necropsy Series. According to these criteria for pathologic diagnosis, examination of autopsy protocols from the Washington University and City Hospital institutions revealed 398 cases with postmortem lesions of syphilitic cardiovascular disease. There were 459 adult hearts showing lesions attributed to rheumatic infection. Eight of the hearts were thought to show coincident syphilitic and rheumatic involvement. The percentage of combined lesions in this series, while small, nevertheless would seem to be of significant magnitude. Of the hearts showing syphilitic involvement, 2.01 per cent showed endocardial deformities attributed to rheumatic disease. The larger group of adult hearts showing rheumatic lesions exhibited syphilitic lesions in 1.74 per cent of cases. These figures of incidence are smaller than have been reported by some observers.[26,27,32]

TABLE II

SUMMARY OF CASES AT AUTOPSY WITH LESIONS OF CARDIOVASCULAR SYPHILIS, AND LESIONS PRESUMED TO BE OF RHEUMATIC ORIGIN, SINGLELY AND COMBINED*

Source	No. of Hearts with Syphilitic Disease	No. of Hearts Showing Rheumatic Lesions (Acute or Chronic)	No. of Hearts with Combined Syphilitic and Rheumatic Lesions	Percentage Syphilitic Hearts Showing Rheumatic Lesions	Percentage Rheumatic Hearts with Syphilitic Lesions
Washington University	97	191	3	3.09	1.57
City Hospital	301	268	5	1.66	1.49
Totals	398	459	8	2.01	1.74

* The total number of autopsies from which these cases were gathered included 10,479 at the St. Louis City Hospital and 6,800 from the Department of Pathology of Washington University. The larger number of autopsies performed at the former institution accounts for the greater number of cases of both syphilitic and rheumatic cardiac disease.

The incidence of cases of aortitis and rheumatic valvular heart disease in this study is summarized in Table II.

Description of Hearts Showing Coexistent Lesions. The pathologic changes in the eight hearts and aortas in this series is presented in Table III. All of the hearts showed syphilitic aortitis, in two of which aortic valvulitis (with clinical incompetence of the valve) was noted. Three of the cases exhibited aneurysm of the aorta, in one of which aortic valvulitis was also present. All of the hearts exhibited chronic endocardial changes involving the mitral valve interpreted as rheumatic in etiology. Stenosis of the mitral valve was apparent in six of the hearts. In two specimens (No. I and No. VIII) there appeared to be disease of the valve justifying the diagnosis of rheumatic endocarditis, but without gross stenosis of the valve. In one heart (No. III) mitral stenosis, aortic stenosis and possibly early stenosis of the tricuspid valve were complicated by syphilitic aortitis. In this case the ascending aorta was definitely dilated which might have been interpreted as an aneurysm. Case I exhibited a plaque-like lesion in the left auricular endocardium similar to that described by MacCallum[44] as occurring in the wake of rheumatic infection. Microscopically, the atrial subendocardium at the site of the plaque was thickened and showed large cells arranged at right angles to the endocardial surface suggesting the "palisades" of cells described by Clawson and his co-workers.[41]

None of the cases in this study exhibited myocardial or endocardial Aschoff nodules. One specimen (Case II) showed perivascular fibrosis with accumulations of large cells arranged so as to resemble old Aschoff bodies.

TABLE III

SUMMARY OF PATHOLOGIC LESIONS DESCRIBED FOR THE EIGHT CASES PRESENTED IN THIS ARTICLE*

Case	Aortic Lesions (Syphilitic)	Cardiac Lesions (Rheumatic) (Syphilitic)	Remarks
I. M. B. R. Male, age 39	Gross: Ascending aorta dilated; adventitia thickened. Intima marked by many pittings and linear puckering; thickened to one-half thickness of media Histologic: Numerous small medial vessels and distortion of elastic lamellas; lymphocytic infiltration. Adventitia thick and hyalinized; adventitial vessels collared with lymphocytes and plasma cells	Gross: Heart enlarged; weight 485 gm. Plaque-like thickening of left atrial endocardium. Fibrous thickening of edges of mitral valve. Insertions of aortic valve cusps spread by mounds of fibrous tissue Histologic: Atrial subendocardium contained large cells arranged at right angles to endocardium. Muscle vessels showed slight perivascular fibrosis. No Aschoff bodies	Clinical: Positive STS. Polyarthritis 9 yr. previously. Diagnosis of syphilitic heart disease. Died in congestive heart failure Diagnosis: Syphilitic aortitis; chronic endocarditis of mitral valve and left atrium
II E. R. Female, age 38	Gross: Puckered intimal areas of ascending aorta to sinuses of Valsalva. Aorta not dilated Histologic: Adventitia thickened with lymphocytic infiltration of vasa vasorum. Vascularized scars distorting media	Gross: Heart enlarged; weight 750 gm. Left atrial endocardium thick and opaque. Mitral leaves greatly thickened along edges with marked thickening of chorda tendineae. Papillary muscles had ivory color. Mitral orifice "somewhat smaller" than normal. Aortic cusps thickened. Two were adherent; other adjacent cusps were separated Histologic: Perivascular fibrosis with accumulations of myocardiocytes in Aschoff-like nodules; appeared like old Aschoff bodies	Clinical: Mitral diastolic murmur and cardiac enlargement. Positive STS† Diagnosis: Syphilitic aortitis and valvulitis; chronic mitral endocarditis
III B. K. Female, age 68	Gross: Ascending aorta dilated to 100 mm. at a point 5 cm. above aortic orifice. Moderate number of fine pinpoint scars in intima Histologic: Adventitial thickening of ascending portion with marked perivascular lymphocytic and plasma cell infiltration. Medial vascularized scars	Gross: Cardiac enlargement; weight 465 gm. Left atrium dilated. Hypertrophy both ventricles. Mitral valve thickened with nodular margin; commisures partly obliterated; chorda tendineae short and thick. Aortic valve showed shortening of cusps and obliteration of commisures Histologic: Muscle not remarkable. Fibrosis of valve structures. Myocardiocytes in mitral valve	Clinical: Mitral and aortic stenosis and cardiac enlargement. Positive STS.† Asymptomatic neurosyphilis Diagnosis: Syphilitic aortitis; chronic endocarditis of mitral, tricuspid and aortic valves
IV J. F. Male, age 60	Gross: Large fusiform aneurysm of ascending aorta. Small intimal wrinkles. Vascularized media. Intima showed much sclerosis with numerous calcified plaques Histologic: Adventitial thickening with mononuclear cellular infiltration about vessels. Lymphocytic collaring in the vascularized media	Gross: Heart enlarged. Ventricular hypertrophy. Mitral valve cusps thickened with rolled borders and obliteration of commisures. Calcification of mitral ring. Chorda tendineae and papillary muscles not remarkable. Aortic valve showed some widening of ring with fusion of left and posterior cusps; edges of cusps rolled Histologic: Not remarkable	Clinical: Congestive heart failure. Aneurysm recognized. Positive STS.† Diagnosis of syphilitic heart disease. Gave history of migratory arthritis in childhood Diagnosis: Syphilitic aortitis (aneurysm); chronic endocarditis (stenosis) of mitral valve

TABLE III (*Continued*)

Case	Aortic Lesions (Syphilitic)	Cardiac Lesions (Rheumatic) (Syphilitic)	Remarks
V P. DeM. Male, age 45	Gross: Aorta not dilated. Walls of vessel generally thickened. Number of small yellow plaques on intimal surface Histologic: Thickening of adventitia. Vascular media with perivascular round cell infiltration. Atheromatous intimal changes	Gross: Heart enlarged; weight 450 gm. Muscle not notable. Endocardium smooth. Leaves of mitral valve fused and thickened, with orifice of 1 cm. Chorda tendineae thickened; papillary muscles enlarged. Edges valve rough and granular. Other valves appeared normal. Histologic: Perivascular fibrosis of myocardium; thickened vascular mitral valve leaves	Clinical: Death from congestive heart failure. STS† doubtful. History fragmentary Diagnosis: Syphilitic aortitis; chronic endocarditis of mitral valve with stenosis
VI B. T. Aged male. Negro (Exact age unknown)	Gross: Marked widening of ascending aorta, with saccular aneurysm in transverse arch about 13.5 cm. diameter. Intimal scarring. Also many atheromatous plaques Histologic: Advanced intimal thickening with perivascular round cell infiltration. Marked vascularization of media	Gross: Heart "enlarged and hypertrophied." Mitral valve leaflets showed thickening and fusion at edges. Stenosis of valve definite. Few fibrinous vegetations at border. Other valves not remarkable Histologic: Thickened vascular mitral leaves	Clinical: Positive STS.† Cardiac enlargement and failure. No murmurs recorded Diagnosis: Syphilitic aortitis (aneurysm); chronic mitral endocarditis with stenosis
VII D. S. Female, age 45	Gross: Aorta not dilated. Longitudinal intimal furrowing most marked in ascending portion. Many atheromatous plaques Histologic: Thickened adventitia with lymphocytic and plasma cell infiltration about vessels. Vascular media also with collaring of vessels by round cells. Intima thickened	Gross: Heart enlarged. Epicardium 3–4 mm. thick. Mitral valve showed fibrosis and fusion of cusps with restricted orifice which "admits only a finger tip." Other valves and endocardium elsewhere appeared normal. Histologic: Fibrinous pericarditis. Not remarkable regarding endocardial lesions	Clinical: Paretic neurosyphilis; STS† positive and spinal fluid positive for syphilis. No cardiac murmurs recorded Diagnosis: Syphilitic aortitis; chronic mitral endocarditis (stenosis)
VIII M. F. Male, age 45	Gross: Aortic dilatation. Wall thickened; many gray raised plaques and marked wrinkling and furrowing. Mesaorta thickened. Vascularized media Histologic: Marked vascularization of media and adventitia with round cell infiltration and perivascular collaring	Gross: Heart weight 750 gm. Myocardium hypertrophied. Chorda tendineae markedly shortened and thickened. Aortic valve leaves rolled and thickened. Coronary vessels patent Histologic: Marked perivascular fibrosis of myocardium. No Aschoff bodies. Margin of mitral valve thick and cellular	Clinical: Positive STS.† Congestive heart failure. Diagnoses of either syphilitic or rheumatic heart disease Diagnosis: Syphilitic aortitis (aneurysm) and valvulitis; chronic mitral endocarditis

* The eighth case (M. F.) is described in the text. Autopsies on Cases IV, VI and VII were performed in earlier years and exact cardiac measurements were not recorded.

† STS indicates serologic test for syphilis.

COMMENTS

It is widely held that the Aschoff body represents the specific anatomic reaction of cardiac tissues to active rheumatic fever.[39–42] In the absence of Aschoff cells certain endocardial deformities are presumed to result from rheumatic infection. Gross and Ehrlich[42] have brought out the peculiar predilection of the Aschoff cell collections for the mitral and aortic valvular endocardium and for the endocardial and muscular structures of the left atrium and posterior wall of the left ventricle. Therefore, endocardial scarring and distortion and the perivascular fibrosis, particularly in the left heart, may represent residual effects of the disease. In the wake of the acute responses to rheumatic infection a continuous endocardial disease may be established.[43] The valvular leaves become thickened, retracted and adherent to each other, the fibrous thickening being more marked, usually, near the free edges of the membrane. Vascularization of the auricular surfaces of the auriculoventricular valves (most frequently the mitral) is commonly seen. The commisural structures may be densely adherent and even totally obliterated, with thickening extending to the chorda tendineae. Various extensive secondary changes such as calcareous deposition and dense hyalinization may occur over a period of time.[43] The familiar gross lesions of mitral and aortic stenosis are thus formed; the other valves are more rarely involved. If narrowing of the valve orifices is not marked, scarring and retraction of the leaflets together with the other distortions noted heretofore may leave little doubt that the fundamental pathologic process is the same. Furthermore, it has been suggested[45] that Aschoff nodules and histories of rheumatic infection may be found in instances showing calcific nodular aortic stenosis or other advanced endocardial deformities so that the presence of such lesions may be regarded as presumptive evidence of past rheumatic disease. Although it is quite possible that certain valvular lesions (e.g., aortic stenosis) may result purely from degenerative processes,[46] the question of rheumatic etiology often cannot be eliminated and such well defined changes as mitral stenosis and certain endocardial distortions leading to aortic stenosis and (frequently) to incompetence are assumed by most clinicians and by many pathologists to be rheumatic in origin. It is largely upon the latter premise that the pathologic diagnosis of "chronic rheumatic heart disease" was made in our series of cases.

It is of some interest that diseases as common as syphilitic disease and also rheumatic inflammation of the cardiovascular apparatus do not complicate each other more frequently. Indeed, combined syphilitic-rheumatic lesions were noted in only 2 per cent or less of cases of each kind in this series and in comparably low percentages in other series.[32,34,36,37] Lisa and Chandlee,[19] who found combined cardiovascular lesions in a larger percentage of cases of syphilitic cardiovascular infection, suggested that rheumatic inflammation may have been abetted or reactivated by subsequent syphilitic infection. However, patients with acute recurrent or chronic rheumatic carditis are frequently overtaken by fatal cardiac breakdown in earlier adult years. DeGraff and Lingg[37] studying a series of patients who had died of rheumatic heart disease noted the mean age of death at thirty-three years in 644 patients. The authors were led to postulate that persons with rheumatic heart disease may succumb before the lesions of syphilis or arteriosclerosis can develop. In our study the patients had reached middle life or rather advanced years before death occurred. In the light of available evidence it appears probable that both syphilitic and rheumatic processes may be quite independent and that the usually low incidence of combined cardiac infection may be due to the lower incidence of syphilis in patients who have had rheumatic fever and carditis.

The frequency of combined syphilitic and chronic endocardial lesions raises the question of the clinical recognition of these coexistent defects. Fortunately, most instances of acquired cardiac valvular disease may be

correctly evaluated by appropriate historical data or by the presence of distinctive physical signs. Difficulties in the etiologic interpretation of valvular defects are greater in patients in middle life from whom histories of both syphilis and rheumatic fever are obtained. In such patients aortic insufficiency occurring as a solitary sign may be difficult or impossible to evaluate as to etiology.[4,47] Under these conditions the presence of adjunctive signs of syphilitic or of rheumatic cardiovascular disease (e.g., mitral stenosis or aortic aneurysm) becomes of importance. The entire problem seems well exemplified by the case presented in the text. On review of this case the adjunctive signs of syphilitic and rheumatic heart disease were not accurately judged. The mitral diastolic murmur was interpreted by a number of physicians as the Austin Flint phenomenon.[48] Had the course of the esophagus been studied by barium swallow and left atrial enlargement thus been demonstrated, the diagnosis of mitral stenosis might have been established. Swanson[25] has stated that coexistent luetic and rheumatic lesions may be present when aortic aneurysm, aortic insufficiency and a presystolic apical murmur are present; when mitral stenosis is complicated by aortic regurgitation (in which the mitral murmur appeared first) and clinical evidences of syphilis may be present. He further indicates that the combination may be present when aortic aneurysm and a diastolic murmur occur in a patient giving an adequate history of rheumatic infection. These criteria, in a broad sense, should unmask the clinical possibility.

SUMMARY

Forty-seven instances of syphilitic cardiovascular disease combined with chronic endocardial disease, probably rheumatic in origin, have been noted in the literature and are briefly reviewed.

Among 398 autopsy specimens of syphilitic cardiovascular disease and 459 specimens showing rheumatic heart disease (acute and chronic) at this institution, there were eight specimens exhibiting combined syphilitic aortitis and chronic endocardial lesions judged to be of probable rheumatic origin.

The clinical problem of the recognition of combined syphilitic and rheumatic lesions of the cardiovascular system is illustrated by the case report of a male patient showing clinical evidence of aortic dilatation, aortic insufficiency and a mitral diastolic murmur together with a history of syphilis. Necropsy showed a combination of diseases herein described. It is emphasized that the possibility of coexistent syphilitic rheumatic heart disease must be considered when overlapping evidence of either of the diseases is discovered clinically.

In large autopsy series of either syphilitic or rheumatic hearts the incidence of such combined lesions varies from 1 to 10 per cent.

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Rheumatic Fever and Glomerulonephritis*

A Clinical and Postmortem Study

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IT has been widely accepted that both rheumatic fever and acute glomerulonephritis are due to altered tissue reactivity following beta hemolytic streptococcic infection.[1–4] In glomerulonephritis the primary streptococcal infection occurs in the nasopharynx chiefly. However, nephritis may follow group A beta hemolytic streptococcic infections elsewhere.[4,5] As to rheumatic fever many structures have been incriminated in the rheumatic process in addition to the commonly recognized involvement of endocardium, myocardium, pericardium and the central nervous system (chorea), such as the lungs and the vascular system in general.[6–12] However, scant attention has been given to possible kidney involvement in the rheumatic process. Since both nephritis and rheumatic fever may follow an infection by the identical organisms, this investigation was undertaken to determine the incidence of their occurrence in the same individual.

Baehr and Schifrin[13] commented on the rarity of glomerulonephritis in rheumatic fever. They examined the autopsy protocols of 235 patients of whom 118 had died of acute rheumatic fever and 117 of rheumatic heart disease. They further limited their series by eliminating from consideration those patients among their chronic rheumatics who died past the age of thirty-one, in order to exclude the possibility of arteriosclerotic valve deformities. They found only three cases of glomerulonephritis, an incidence of 1.3 per cent. In the discussion following a paper by Rubin and Rapoport on the cardiac complications of acute hemorrhagic nephritis, Lyttle[14] states that he has seen at autopsy only one case of rheumatic endocarditis and myocarditis with glomerulonephritis in 150 cases. This patient also showed extensive necrotizing arteritis in the kidneys. In a series of 138 young adults, Whitehill, Longcope and Williams[15] noted that five had definite rheumatic heart disease and two had questionable rheumatic heart disease at varying intervals before their nephritis. Rolly[16] found acute nephritis in only 0.67 per cent of several thousand cases of rheumatic fever collected from the literature. He further states that he has seen sixteen cases of simultaneous acute nephritis and rheumatic fever in his personal series of 2,652 cases. Fishberg[17] has seen only two cases of anatomically typical acute glomerulonephritis in patients who died of acute rheumatic fever. In a review of the cardiac complications in acute nephritis Odel and Tinney[18] of the Mayo Clinic noted not a single case of rheumatic heart disease in 136 patients.

On the other hand, Stettner[19] reported hematuria in thirty-three of fifty rheumatic children. Veil[20] contended that an attack of hemorrhagic nephritis had the same significance as the occurrence of polyarthritis in rheumatic fever. Coburn[21] calls hematuria one of the classical signs of rheumatic activity. Loeb[22] stated that in one year alone he had seen fifteen cases of active rheumatic disease associated with acute glomerulonephritis. Evans[23] believed that the rheumatic agent may at times cause a malignant sclerosis of the renal blood vessels, an opinion in which T. Fahr concurs.[24] Goldring[25] calls attention to the frequent presence of albuminuria, cylindruria, white blood

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cells and not uncommonly red blood cells in the urine of patients with acute rheumatic fever. He suggests that this is due to an injury of the glomerular capillaries as the non-specific result of fever. He states further, however, that he has seen two patients at Bellevue Hospital with concurrent acute diffuse glomerulonephritis and active rheumatic carditis. E. T. Bell[26] examined the kidneys of 104 cases of active rheumatic endocarditis with fresh rheumatic vegetations on the valves. He found the glomeruli to be normal in eighty-one cases (77.8 per cent). In one case there was typical advanced diffuse glomerulonephritis. However, in twenty-two cases (21 per cent) the glomeruli showed a moderate but definite diffuse glomerulitis characterized by a definite increase in the number of capillary endothelial cells. He occasionally noted an increase in the number of white blood cells in the glomerular capillaries. The increase in the endothelium and the degree of capillary obstruction were much less prominent than in clinical acute glomerulonephritis but the changes were quite definite nonetheless. There have been two more recent contributions to this question published in the Scandinavian literature. Salvesen[27] found renal complications in forty-four of 212 patients with rheumatic fever but only ten of these showed evidence of acute glomerulonephritis with hypertension and hematuria in addition to proteinuria and casts. This is an incidence of 4.7 per cent. He further examined the records of 287 patients with acute or chronic nephritis; twenty-nine gave a history of rheumatic fever. However, in six the relationship between rheumatic fever and nephritis was such that he felt justified in making a diagnosis of rheumatic nephritis (incidence of 2 per cent). He defines rheumatic nephritis as a nephritis which develops during, shortly after or, rarely, immediately before an attack of rheumatic fever. Ehrstrom[28] studied 120 cases of acute diffuse glomerulonephritis during the period 1935 to 1939. He discusses twenty-two of these cases in detail. Fourteen conform to Salvesen's definition of rheumatic nephritis. In the other eight cases the patients had both polyarthritis and nephritis but at varying intervals. The time intervals varied between two and nine years in these latter cases. Thus among the 120 cases of nephritis "rheumatic nephritis" occurred in 11.5 per cent. Polyarthritis and nephritis occurred in the same person in 18.3 per cent.

METHOD OF STUDY

The present analysis consists of two parts. First, we have studied the records of all patients discharged from the Massachusetts General Hospital during the ten-year period 1937 to 1946 with the diagnosis of acute hemorrhagic nephritis. Secondly, we examined the autopsy protocols of those patients of the House of the Good Samaritan who died during the past twenty-five years and who had rheumatic heart disease. During this period approximately 3,000 patients with rheumatic fever have been hospitalized at the House of the Good Samaritan.

RESULTS

One hundred seventeen clinical records having a discharge diagnosis of acute glomerulonephritis were examined. The incidence at each age is given in the following tabulation:

Age....	0–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–80
No. of Cases.	21	30	29	11	8	3	2	2	3	8

One patient, aged six, developed cardiac murmurs during an admission for acute nephritis. The nephritis cleared under routine treatment but his cardiac status progressed to organic mitral disease with stenosis. Another young schoolboy, aged fourteen, developed recurrent acute rheumatic fever during an attack of acute hemorrhagic nephritis. Three other male patients entered in confused states and could give no adequate history. All three died and were examined post mortem. One had acute and subacute glomerulonephritis with calcare-

ous stenosis and Aschoff bodies in the aortic leaflets. The second had subacute diffuse glomerulonephritis with rheumatic heart disease and subacute bacterial endocarditis. It should be noted that the nephritis was a diffuse glomerulonephritis and not the embolic type often seen with subacute bacterial endocarditis. The third had marked acute glomerulonephritis with extensive glomerular endothelial proliferation, as well as epithelial proliferation and crescent formation in addition to acute rheumatic endo- and myocarditis superimposed on chronic rheumatic heart disease with mitral and aortic involvement. Two patients had polyarthritis with their acute nephritis with clearance of both at the time of discharge. No long term follow-ups are available on these latter two.

CASE REPORTS

L. P. M. (Massachusetts General Hospital, No. 42104), a six year old white boy, was admitted on October 20, 1931, because of swollen neck glands and a general feeling of ill health. Two weeks before entry he had contracted a cold and fever. The following day he complained of a sore right knee which, however, was not swollen or hot but was slightly tender to palpation. Walking was painful. The fever subsided on bed rest but then cervical adenitis developed. On entry to the hospital the patient complained of anorexia, vomiting, headaches and nocturia with dark-colored urine of one week's duration. The night before admission he had a spontaneous epistaxis. The family history was non-contributory. Past history revealed a story of numerous upper respiratory infections which finally led to a tonsillectomy and adenoidectomy at the age of five. Physical examination on admission revealed the following positive findings: carious teeth, moderate enlargement of the heart, P_2 greater than A_2 and a rough systolic murmur at the cardiac apex. The blood pressure varied from 160/120 on entry to 95/60 at the time of discharge. The joints were negative to objective examination. Urinalysis showed albumin, numerous white blood cells, many red blood cells and at times granular and cellular casts. Serum non-protein nitrogen on entry was 47 mg. per cent and 24 mg per cent at the time of discharge. Chest x-ray revealed enlargement of the heart to the left with some congestion of the lungs. The patient was treated with bed rest and digitalis, with gradual clearing of his symptoms. He was discharged from the hospital seven weeks after admission and was followed up in the outpatient department where it was noted that he had a persistent low grade fever, tachycardia and cardiac enlargement. Therefore, he was readmitted three months after his first discharge with the diagnosis of active rheumatic fever. Physical examination at this time showed a harsh mitral systolic murmur and a late crescendo diastolic murmur at the apex. The blood pressure was 115/68. The urine was negative. After a period of bed rest the patient was discharged and has been followed up in the outpatient department for fifteen years. A year before this writing it was noted on a chest x-ray that calcification of the mitral valves had occurred accompanied with enlargement of the left auricle. However, the patient has been in good health and has graduated from college.

J. M. (Massachusetts General Hospital, No. 228998), a fourteen year old schoolboy, entered the hospital because of a "flame-like" pain in his para-umbilical region which began six days prior to admission and became increasingly severe. Ten days prior to admission his left ankle became red, swollen and tender and he was unable to walk. At the same time he began to have "stiffness" in most of his joints. He also had vomiting and malaise. His past history was notable in that he had chorea at the age of six and thirteen followed with rheumatic heart disease. Physical examination revealed a poorly developed, poorly nourished boy acutely and chronically ill. His temperature was 101°F., pulse 96, respirations 32 and blood pressure 120/85. His face appeared puffy. The heart was grossly enlarged to the left. P_2 was loud. There were a grade 3 systolic blow and a rumbling mid-diastolic murmur at the apex. The joints were negative to examination. Urinalysis showed 2 plus albumin, two white blood cells per high power field, eight to ten red blood cells per high power field, and a few granular and hyaline casts. The sedimentation rate was 1.2 mm./minute (three times normal). Serum non-protein nitrogen was 23 mg. per cent. The electrocardiogram was normal. On bed rest the patient's symptoms improved and the intensity of his apical murmurs decreased. He was discharged after a total hospital stay of six months. He was followed up for one year after discharge when physical examination revealed a loud M_1,

an audible third heart sound and a short crescendo presystolic murmur at the apex. His urine was normal except for the persistence of a trace of albumin.

The two patients (Massachusetts General Hospital, No. 104727, 189779) in whom polyarthritis developed during typical acute nephritis were both males. Both had uneventful courses and no evidence of heart disease. Neither patient has been seen since discharge. Their ages were thirty-two and thirty.

The three patients who died and were examined postmortem were all men, aged forty-one, fifty and fifty-one (Massachusetts General Hospital, No. 194024, 349199, 128352).

Thus there is an over-all incidence of 6.0 per cent of polyarthritis or rheumatic heart disease in this clinical series of acute glomerulonephritis. In 2.5 per cent there was a simultaneous occurrence of acute rheumatic fever and acute glomerulonephritis. Of patients exhibiting the clinical picture of acute glomerulonephritis who came to autopsy, 1.7 per cent had, in addition, rheumatic heart disease. Of this clinical series, 1.7 per cent had polyarthritis but without demonstrable cardiac involvement during their hospitalization.

For the second part of this analysis 188 autopsy protocols of patients who had had rheumatic fever or rheumatic heart disease were examined from a clinical series of over 3,000 patients admitted to the House of the Good Samaritan since 1921. The fatalities were mostly children or adolescents who succumbed to rheumatic fever. One hundred sixty-six had no primary glomerular involvement; five had acute glomerulonephritis; four had chronic glomerulonephritis, one had thrombotic glomerulonephritis and one had marked renal arteriolitis said to be consistent with rheumatic involvement of this organ. Seven patients had what was characterized as glomerulitis. In these cases there was proliferation of the glomerular epithelium but not of sufficient degree to warrant the diagnosis of glomerulonephritis. Three of the five patients with acute glomerulonephritis had rheumatic fever at time of death. The other two died of the effects of their cardiac involvement. Three were males and two females. The four patients with concomitant chronic nephritis were females; of the seven cases with glomerulitis, six were females and one male. The oldest patient in this series was thirty-five, and the great majority were under twenty-five years of age. Thus 3 per cent of young patients with rheumatic carditis had, in addition, acute glomerulonephritis at the time of death, an additional 2 per cent had chronic nephritis at demise and 3.7 per cent showed mild glomerulitis.

COMMENTS

Since both acute glomerulonephritis and acute rheumatic fever often follow an infection with a group A beta hemolytic streptococcus, it seemed likely on theoretic grounds that the kidneys would show signs of involvement in rheumatic fever and that rheumatic fever might be fairly frequent during acute glomerulonephritis. The reported simultaneous occurrence of glomerulonephritis and rheumatic fever varies from no cases[18] to 4.7 per cent.[27] One author, however, reported an incidence of 11.5 per cent of so-called "rheumatic nephritis."[28] So high a figure has been encountered only once in the literature. In our series the incidence was 2.5 per cent when the clinical records of patients with acute glomerulonephritis were examined, and 3.0 per cent when the autopsy protocols of patients dying of rheumatic fever and heart disease were examined. Although these percentages seem low, they may be significant for they represent the simultaneous occurrence of two diseases both related as to inciting agent. In addition chronic glomerulonephritis appeared in an additional 2 per cent during the life histories of our young patients dying from rheumatic heart disease. Thus it seems likely that if a large group of patients with rheumatic heart disease were followed up for their life span, an even greater number would ultimately give evidence of chronic nephritis either clinically or at post mortem. Since chronic glomerulonephritis is also believed to be initiated by a group A beta

hemolytic streptococcic infection, its presence is as significant as acute nephritis.[4]

SUMMARY AND CONCLUSIONS

The association of rheumatic fever and glomerulonephritis has been reviewed and a further study made of their occurrence in a clinical and postmortem series. The clinical series consists of 117 patients with acute glomerulonephritis studied at the Massachusetts General Hospital during the decade from 1937 to 1946. The postmortem series consists of 188 autopsy protocols from the House of the Good Samaritan where approximately 3,000 children and adolescents with rheumatic fever and heart disease have been studied and followed up since 1921.

Acute glomerulonephritis and acute rheumatic fever occurred simultaneously in 2.5 per cent of the series of clinically diagnosed acute nephritis (117 cases). An additional 1.7 per cent had rheumatic heart disease. Three per cent of the rheumatic series studied at post mortem (188 cases) had acute glomerulonephritis. Chronic nephritis was present in an additional 2 per cent.

Thus in the nephritis series 4.2 per cent had acute or chronic rheumatic involvement of the heart while in the rheumatic series 5 per cent had glomerulonephritis, acute or chronic.

Nephritis occurs somewhat more frequently in patients with rheumatic fever and rheumatic heart disease than is usually suspected, and conversely, involvement of the heart may occur despite predominant involvement of the kidneys in certain cases of nephritis. Although the beta hemolytic streptococcus is the most frequent precipitating agent in both diseases, the determining factor as to organ susceptibility is unknown.

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Blood Levels of Urea Nitrogen, Phenol, Guanidine and Creatinine in Uremia*

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UREMIA has been defined as "the symptom-complex resulting from renal insufficiency and accompanying the retention of urinary constituents in the organism"; further, "no group of symptoms is to be considered as uremic in nature unless it occurs in the presence of abnormally high non-protein nitrogen in the blood."[1] A single blood constituent has long been sought as the causative agent of the symptoms of uremia. Practically every known blood and urinary component has at one time or another been thought to be the important factor. The various theories which have attempted to explain the uremic symptom-complex on the basis of the retention of a single substance have not been supported by either adequate clinical or chemical proof.[2] There is, on the other hand, evidence that one or more of these components may play a role in different phases of this syndrome.

The manifestations of uremia in the central nervous system are believed by Mason et al.[3] to be the resultant of antagonism between depressive and excitatory stimuli. They have found that in experimental animals a "central" deficit of calcium ion appears to be an important cause of increased neuromuscular irritability. This deficit arises as a result of the accumulation of substances such as phosphates which form relatively un-ionized calcium salts. In patients as well as dogs, muscular twitching is abolished by the intracisternal injection of calcium salts in amounts completely ineffective intravenously. In spite of a "central" deficit of calcium ions, however, twitching is not always observed in uremic patients and conversely, with adequate cerebrospinal calcium, it may still occur. Elevation of phenol in cerebrospinal fluid has been identified with a depressant or narcotic effect producing weakness, apathy, stupor, coma and disorientation.[4] Muscular twitching and increased blood pressure, resulting from calcium deficiency produced by intracisternal injection of phosphate, may be completely inhibited by the previous administration of phenol, given either intracisternally or intravenously.

Becher[5] believes that although the uremic symptom-complex is dependent on many substances the role of phenols and other aromatic compounds is most important. These substances are formed in the body as the result of deamination, decarboxylation and oxidation of the aromatic amino acids (tyrosine, tryptophane and phenylalanine). Whether free phenols are formed in normal intermediary metabolism or as a result of bacterial action in the intestine is not as yet clear. Phenols are absorbed from the gastrointestinal tract and detoxified by conjugation with sulfuric or glycuronic acid. The efficiency of their detoxification depends on the normal functioning of liver, intestines and kidneys.[6] Dickes[7] and Roen[8] have reported that the blood levels of phenol more closely paralleled the total uremic symp-

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toms in patients than any other blood constituent. On the other hand, Nesbit, Burk and Olsen[9] found that while the level of blood phenol was elevated in uremia no parallelism was noted with the intensity of uremic symptoms. Recently Wallace, Little and Bobb[10] have concluded that retention of phenolic compounds is of little or no significance in producing signs of nervous system depression in the uremia of dogs.

Guanidine* and/or its derivatives have also been believed to play a role in central nervous symptoms of uremia, Foster[11] and others[12] finding increased amounts in the blood of uremic patients. Their early work was hampered by the lack of specific methods for the determination of guanidine but with the description of more satisfactory methods their observations have been confirmed.[3] Guanidine has been considered to be the physiologic antagonist of calcium; indeed, the dysfunction of the nervous system produced by guanidine can be abolished by adequate amounts of calcium salts. Depending on the degree of accumulation of guanidine, however, different symptoms may be elicited. In dogs, while moderately high levels are accompanied by neuromuscular symptoms, excessively high levels produce depression similar to that caused by phenol. Low levels of guanidine are associated with gastrointestinal and respiratory symptoms.

The gastrointestinal manifestations of uremia have been attributed to two factors. First, guanidine intoxication produces gastroenteritis, vomiting, diarrhea and muscular twitching. This relationship has been demonstrated experimentally in dogs.[3] The amounts of guanidine used were greatly in excess of those ever encountered in terminal human uremia. Second, retention of urea in blood is considered to play an important role. The amount of urea retained is insufficient to produce a primary toxic action. Leiter[13] has shown that urea in quantities up to 1 per cent of the total body weight may be injected before the onset of typical uremic symptoms. Furthermore, in patients with renal insufficiency little parallelism exists between the height of blood urea and the intensity of uremic symptoms.[1] Urea retention may affect the overall picture by augmenting hydration[14] and by increasing the osmotic pressure of body fluids.[15] Finally, bacterial decomposition of urea to ammonia and ammonium salts causes stomatitis, gastritis and colitis.[16] Phenol and creatinine have not been found to be of importance in the pathogenesis of gastrointestinal symptoms.

In the present study, blood levels of phenol, urea nitrogen, guanidine and creatinine have been determined in a series of hospital patients, and intercorrelations made with respect to degree and type of symptom and disease. In this way an attempt was made to discover whether any single parameter or a combination of them could be used clinically as an index of uremia.

METHODS

Thirty milliliters of venous blood were obtained from 148 hospital patients and control subjects in the fasting state, potassium oxalate being used as anticoagulant. Blood urea nitrogen was determined by the method of Barker[17] and the level of phenol by the method of Bernhart and Schneider,[18] calculated as free phenol. Creatinine was estimated by the method of Folin and Wu.[19] The level of guanidine was obtained by a modification of the method of Pfiffner and Meyers,[20] correcting for creatine and creatinine, the results being expressed as a function of color produced by the free base itself.*

Two groups of patients were included; the first had known renal disease, with or without elevation of non-protein nitrogen, and the second a disease known to be associated with secondary renal damage. The control subjects were obtained at random from the hospital staff; all were in good health. The sex distribution of

* The term guanidine as used here denotes the color produced by the modified method of Pfiffner and Meyers, using guanidine as a standard and correcting for creatine and creatinine. It is recognized that other compounds may produce a color with this test but values will be reported as mg. per cent of guanidine.

* Chemical methods were checked continually throughout the study and each analysis was usually done in duplicate. The average recoveries of pure compounds added to blood were as follows, urea nitrogen—98.3 per cent, phenol—108.1 per cent, guanidine—99.9 per cent and creatinine—103.5 per cent.

both groups was approximately equal with an age distribution of twenty to seventy-six years.

In attempting to evaluate the presence and degree of severity of uremia it has been regarded as a clinical entity. Most authors have defined this symptom-complex by including in their criteria some statement as to the blood level of urea or non-protein nitrogen. Since one of the objects of this study was an attempt to correlate clinical findings with blood levels of various substances, all chemical determinations have been disregarded in defining the clinical uremic state. From a careful study of the literature an arbitrary classification of uremic signs and symptoms has been devised as follows: (1) neuromuscular and mental, (2) gastrointestinal, (3) skin and (4) metabolic. These groups have been subdivided and are found in Table I. Evaluation of each of these symptoms and signs has been made, with gradations of 0 to ++++. In this way the severity of uremia has been defined so that a numerical expression for the purpose of comparison with chemical values is possible. This method with its limitations in accuracy introduces a factor of error into each comparison.

TABLE I
SIGNS AND SYMPTOMS OF UREMIA

Neuromuscular and Mental	Metabolic	Gastro-intestinal	Skin
Headache	Weakness	Stomatitis-parotitis	Itching
Twitching and tremor	Weight loss	Anorexia	Hemorrhagic tendency
Dizziness	Anemia	Nausea and vomiting	Frost
Reflex changes	Hypertension	Diarrhea	
Apathy	Pericarditis		
Stupor			
Coma			
Psychosis			
Restlessness			
Convulsions			
Visual disturbances			
Hiccough			

Another approach, which may have greater clinical value, has been to assign a given weight to symptoms based on their severity. (Table II.) It is recognized that many of the signs and symptoms of uremia are common to those of accompanying disease states. For example, some of the symptoms of hypertensive encephalopathy closely parallel those of uremia. Therefore, symptoms which can be explained either on the basis of uremia or the accompanying disease have been given a value of one. The remaining signs and symptoms, which can be divorced from other causes, have then been weighted in regard to their severity as follows: 0 symptoms—0 to 4, + symptoms—5 to 9, ++ symptoms—10 to 13, +++ symptoms—14 to 17 and ++++ symptoms—18 and up. Thus weighted and unweighted clinical symptoms can be evaluated against chemical findings.

TABLE II
WEIGHTED UREMIC SYMPTOMS

1. Symptoms common to uremia and causal disease:
   Headache, dizziness, apathy, stupor, coma, anorexia, visual disturbances, nausea and vomiting, anemia, weakness, weight loss, itching associated with jaundice
2. Symptoms appearing early in uremia:
   Twitching and tremor, reflex changes, psychosis, listlessness, restlessness
3. Symptoms appearing in the intermediate phase of uremia:
   Diarrhea, itching, hiccough, hemorrhagic tendency
4. Symptoms appearing late or terminally in uremia:
   Convulsion, stomatitis, parotitis, frost

TABLE III
AVERAGE VALUES FOR BLOOD UREA NITROGEN, GUANIDINE AND CREATININE WITH STANDARD DEVIATIONS*

Uremic Symptoms	No. of Patients	Urea Nitrogen (mg. %)	Phenol (mg. %)	Guanidine (mg. %)	Creatinine (mg. %)
Normals	29	15.0 ± 3.9	0.78 ± 0.13	0.178 ± 0.052	1.6 ± 0.26
0	53	43.7 ± 28.9	1.01 ± 0.37	0.305 ± 0.142	3.3 ± 2.3
+	25	77.3 ± 49.7	1.06 ± 0.40	0.425 ± 0.253	5.9 ± 4.6
++	20	97.5 ± 41.0	1.39 ± 0.47	0.614 ± 0.360	8.5 ± 4.4
+++	9	193.9 ± 69.6	2.27 ± 0.44	1.192 ± 0.446	16.2 ± 6.3
++++	12	163.5 ± 64.3	2.36 ± 0.64	1.203 ± 0.368	18.8 ± 7.0

* Uremic symptoms are unweighted and expressed arbitrarily from 0 to ++++ in severity.

RESULTS

Table III shows the average values for blood urea nitrogen, phenol, guanidine and creatinine for twenty-nine normal subjects and 119 hospital patients. Patients have

been divided into five groups with reference to their unweighted uremic symptoms. While it is true that for each parameter a definite increasing tendency is observed, the size of the standard deviations of the separate groups definitely rules out any direct correlation with the increasing severity of symptoms. In fact, in each group there is an almost complete overlapping of the results. If the same data are re-evaluated on the basis of weighted uremic symptoms, even less correlation is noted.

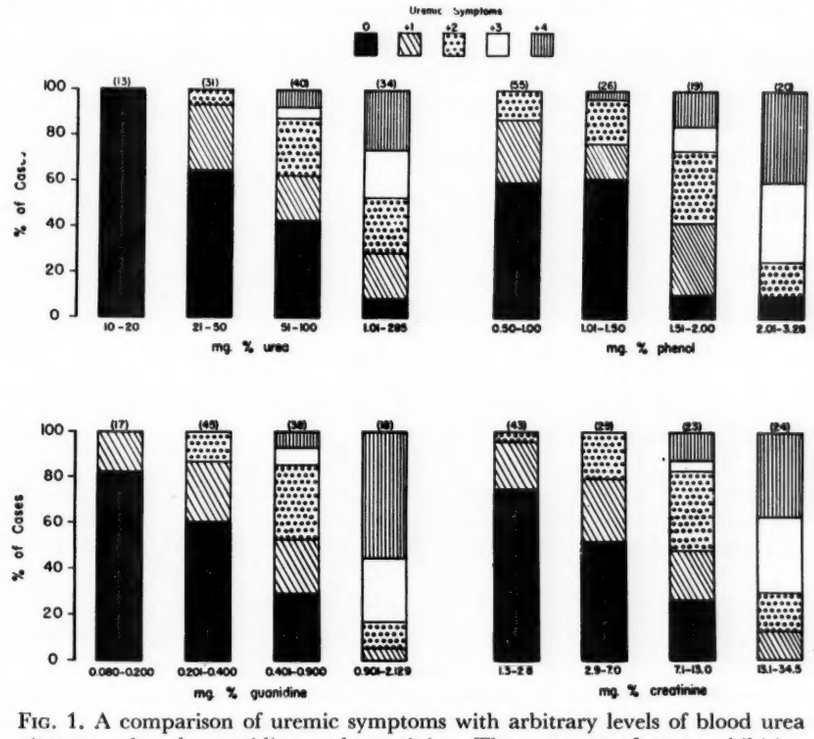

FIG. 1. A comparison of uremic symptoms with arbitrary levels of blood urea nitrogen, phenol, guanidine and creatinine. The per cent of cases exhibiting varying degrees of uremic symptoms is plotted against the level of the blood constituent. The numbers in parentheses on top of the bars refer to the total number of cases in the group.

A breakdown of each of the four chemical variants into four arbitrary levels and a plot of the per cent of cases exhibiting varying degrees of unweighted uremic symptoms is shown in Figure 1. In each group a very rough relation is seen between the severity of uremic symptoms and the level of each constituent. It should be noted that the relationship is not striking; for example, there are patients showing extremely high levels of phenol and urea nitrogen without any uremic symptoms. Conversely, even with comparatively normal levels of phenol, guanidine and creatinine, severe uremic symptoms are found. This breakdown shows still less agreement between clinical and chemical findings when the weighted uremic symptoms are plotted in the same manner.

Table IV shows a comparison of the weighted versus unweighted uremic symptoms with the blood level of phenol. Similar results have been obtained with blood urea nitrogen, guanidine and creatinine.

Table V is an attempt to relate the degree of uremia and level of blood constituents studied with various disease and symptom groups. The best correlation appears with primary renal disease. As uremic symptoms increase, the levels of urea nitrogen, phenol and guanidine all rise in a proportionate manner. However, at the + + + + level all of the chemical parameters fall to a slight extent. In each of the other disease groups the relationship is very poor. Three symptom groups have also been analyzed—central nervous system depression, gastro-

intestinal symptoms and elevation of blood pressure. In each the blood levels of urea nitrogen, phenol and guanidine show no consistent rise or fall with the intensity of symptoms or findings. If one tries to relate the levels of these constituents to changes in uremic symptoms in a single patient the results are more encouraging. Thirty-six patients have been studied for a prolonged period. In Table VI are shown five representative patients who have been followed through the course of their disease. As symptoms increase the urea nitrogen, phenol, guanidine and creatinine all increase. Conversely, these chemical constituents of blood tend to revert toward normal levels as uremic symptoms disappear. It is true that there is no strict proportionate rise or fall in any of the components studied which can be explained on the basis of the clinical

TABLE IV

ANALYSIS OF WEIGHTED AND UNWEIGHTED UREMIC SYMPTOMS WITH REFERENCE TO BLOOD PHENOL LEVEL*

Phenol (mg. %)	No. of Patients	Uremic Symptoms									
		0		+		++		+++		++++	
		U	W	U	W	U	W	U	W	U	W
0.50–1.00	55	60.0	23.4	27.3	56.4	12.7	16.4	0.0	3.6	0.0	0.0
1.01–1.50	26	61.6	19.2	15.4	42.3	19.2	23.1	0.0	15.4	3.8	0.0
1.51–2.00	19	10.5	5.3	31.6	31.6	31.6	36.8	10.5	0.0	15.8	26.3
2.01–3.28	20	10.0	0.0	0.0	35.0	15.0	35.0	35.0	20.0	40.0	10.0

* Normal blood phenol level was 0.78 ± 0.13 mg. per cent. Four arbitrary groups have been made to include the range of experimental data. The uremic symptoms are graded as 0, +, ++, +++, and ++++ by unweighted (U) and weighted (W) analyses. Numerical values refer to per cent of the group in question exhibiting the columnar uremic symptoms.

TABLE V

RELATION OF DEGREE OF UREMIA AND LEVEL OF BLOOD CONSTITUENTS TO VARIOUS DISEASE AND SYMPTOM GROUPS*

Disease or Symptom Group	Urea Nitrogen (mg. %)					Phenol (mg. %)					Guanidine (mg. %)				
	Uremic Symptoms														
	0	+	++	+++	++++	0	+	++	+++	++++	0	+	++	+++	++++
Disease Group:															
Prerenal azotemia	50.2 (18)	93.2 (8)	67.3 (10)	.....	.....	0.93	1.35	1.11	....	....	0.37	0.48	0.44	....	....
Primary renal disease	57.2 (10)	73.9 (12)	108.2 (13)	177.6 (9)	163.5 (15)	0.98	1.03	1.54	2.34	2.36	0.30	0.40	0.70	1.31	1.21
Postrenal obstruction	49.3 (13)	57.1 (6)	75.2 (4)	.....	.....	1.00	1.01	1.01	....	....	0.31	0.42	0.46	....	....
Essential hypertension	47.7 (9)	65.8 (6)	102.4 (3)	.....	.....	1.56	0.70	1.70	....	....	0.37	0.30	0.44	....	....
Malignant hypertension	64.6 (3)	148.1 (5)	64.1 (3)	46.3 (9)	93.6 (8)	0.97	1.49	1.23	1.95	1.59	0.29	0.91	0.40	0.94	0.98
Symptom Group:															
CNS depression	....	109.1 (11)	87.6 (13)	161.2 (5)	152.0 (16)	....	1.24	1.29	2.18	2.28	....	0.66	0.43	1.08	1.12
Gastrointestinal symptoms	....	72.1 (12)	100.0 (16)	221.1 (9)	181.0 (8)	....	1.06	1.35	2.33	2.69	....	0.38	0.62	1.17	1.19
Elevated blood pressure	....	119.0 (32)	77.1 (16)	66.4 (14)	95.3 (22)	....	1.62	1.23	1.12	1.43	....	0.73	0.33	0.45	0.64

* Values given in table are average results expressed in mg. per cent. Figures in parentheses are number of cases in each group.

evaluation of symptoms. The point remains that these blood parameters vary in some way with the degree of uremic symptoms and the levels vary greatly from patient to patient.

TABLE VI

LEVELS OF BLOOD UREA NITROGEN, PHENOL, GUANIDINE AND CREATININE AT DIFFERENT UREMIC SYMPTOM LEVELS IN THE SAME PATIENT*

Case No.	Diagnosis	Uremic Symptoms	Urea Nitrogen (mg. %)	Phenol (mg. %)	Guanidine (mg. %)	Creatinine (mg. %)
26	Hypertension, nephrosclerosis	+	89.0	1.40	0.72	11.6
		++++	92.5	1.40	0.94	12.7
		++++	86.9	1.54	0.88	15.8
		+++	88.9	1.76	1.16	14.3
		++++	101.5	1.85	1.11	15.6
53	Benign prostatic hypertrophy	++	104.5	1.15	0.62	7.6
		0	38.3	0.85	0.34	2.1
59	Pyoureter and renal lithiasis	0	37.4	0.95	0.39	4.0
		+	82.9	1.16	0.69	4.2
		+	38.3	0.69	0.32	1.7
		0	31.1	0.65	0.27	1.7
71	Congenital cystic disease of kidneys, hypertension, diabetes mellitus	+	138.1	1.59	0.76	14.4
		+	134.1	1.60	0.75	13.7
		++	142.2	2.22	0.82	13.6
		+++	246.0	2.78	1.36	23.3
81	Pyloric obstruction, diabetes mellitus, peptic ulcer	+	161.5	1.00	0.62	11.5
		+	121.3	1.24	0.41	8.6
		0	113.0	1.16	0.36	5.7

* Samples of blood were obtained at average intervals of ten days (range, 3–65 days).

COMMENT

In attempting to compare clinical symptoms of uremia with various blood constituents it becomes obvious that the blood levels of urea nitrogen, phenol, guanidine and creatinine are increased in uremia but that there is no strict correlation with the intensity of symptoms. Experimental uremia has been produced in dogs using each of these compounds; in every case an imperfect picture was obtained.[3,13] Uremic symptoms produced by urea necessitates the injection of huge amounts. Phenol produces uremic symptoms characterized by central nervous system depression. In human beings levels of phenol were not appreciably different in those with central nervous symptoms as compared to those with gastrointestinal symptoms (Table v) or with anemia. In this study guanidine retention perhaps more clearly follows the uremic state than does accumulation of any of the other constituents. It should be noted that the blood guanidine level of patients with elevated blood pressure bears no relation to the degree of hypertension. Guanidine has been shown to cause in dogs a nearly complete picture of uremia; however, the results have been somewhat erratic depending on the dosage. In any case the blood levels producing symptoms in experimental animals are much higher than those found in our study of human subjects.

In Figure 2 a scatter-graph has been made in which the values in mg. per cent of blood urea nitrogen, phenol, guanidine and creatinine have been plotted against each other. In this correlation we are concerned solely with the levels of these blood constituents, irrespective of clinical uremic symptoms. If the level of any of the four compounds studied had any direct relation to any other one, as postulated in the multiple retention theory of uremia, a good correlation should be noted. As can be seen

the correlations are very poor. Thus on a purely chemical basis no sound rationale for the assumption that two or more of these constituents *per se* are the indices of uremia can be formulated.

In regard to the disease state itself, it is interesting that all four of these parameters increase somewhat progressively in primary renal disease. In prerenal azotemia and postrenal obstruction the blood urea nitro-

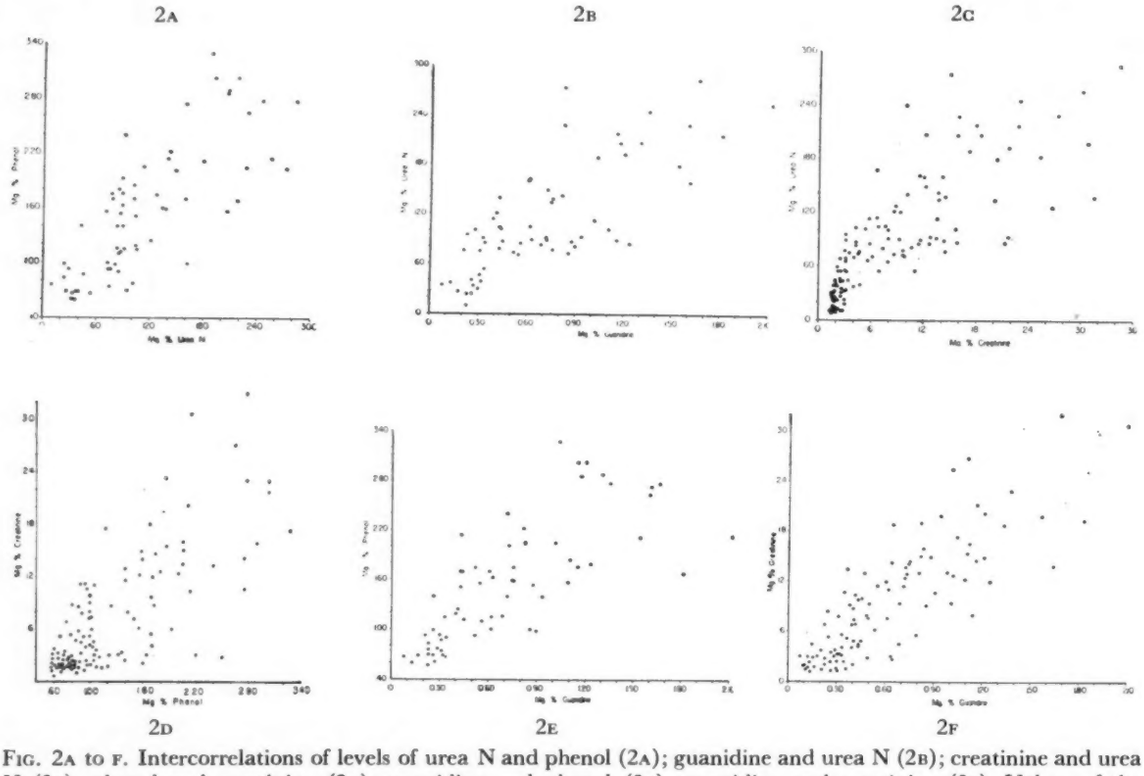

FIG. 2A to F. Intercorrelations of levels of urea N and phenol (2A); guanidine and urea N (2B); creatinine and urea N (2C); phenol and creatinine (2D); guanidine and phenol (2E); guanidine and creatinine (2F). Values of the various blood constituents expressed in mg. per cent have been plotted against each other with no reference to uremic symptoms.

An accurate clinical evaluation of the uremic state is important. Numerous investigators have considered various symptoms as the most relevant. A comparison of the intensity of symptoms based on weighted or unweighted evaluations may lead to almost contradictory impressions in regard to the clinical picture. It is recognized that these impressions are subjective and arbitrary and therefore a source of error is introduced which might completely hide any relationship. In Table III it can be seen that the chemical values for the varying degrees of uremic symptoms are mutually overlapping. It must be noted, however, that a definite trend of increasing levels of blood urea nitrogen, phenol, guanidine and creatinine with increasing uremic symptoms is observed and cannot be ignored.

gen increases but the levels of guanidine, creatinine and phenol are much lower and show a less consistent rise. A comparison of essential and malignant hypertension shows that in both the blood levels of all four parameters increase to only moderately high levels with severe uremic symptoms, and therefore on a purely chemical basis essential and malignant hypertension are indistinguishable.

CONCLUSION

Blood levels of urea nitrogen, phenol, guanidine and creatinine have been determined in a control group of twenty-nine normal subjects and a hospitalized group of 119 uremic patients. The values for the control group fell within a very narrow range which agrees well with those previ-

ously reported. In the uremic patients, as symptoms increased there was a tendency for all four chemical constituents to increase. The range was very broad, however, and no definite correlations can be made. Blood levels of phenol could not be correlated with central nervous system depression nor could those of guanidine be correlated either with gastrointestinal stimulation or degree of elevation of blood pressure. Intercorrelation of the levels of the four chemical constituents was very poor.

Depending on the weighting and clinical evaluation of the uremic symptom-complex, varying degrees of intensity of uremia could be obtained. The data, however, are inconsistent with the theory of the interdependency of uremic symptoms with blood levels of urea nitrogen, phenol, creatinine and guanidine. Uremia remains a clinical entity without any direct known chemical basis.

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Experimental Studies on the Irritable Colon*

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In many gastrointestinal clinics the benches are very largely occupied by a group of patients who suffer chronically with abdominal pain, constipation and diarrhea. In these patients the combined efforts of the internist, roentgenologist and clinical pathologist fail to reveal any organic cause for the disorder. Usually the only objective evidence of disordered function is the proctoscopic finding of spasm, engorgement and excessive mucous secretion in the sigmoid colon. The syndrome has been given a variety of names; the most popular among them are "irritable colon" and "mucous colitis."

This intestinal disorder, in spite of its prevalence, has attracted less attention from medical investigators than it deserves. Granted that it has probably never caused the death of a patient, nevertheless the discomfort is such that some patients wish they were dead and many others are disabled as markedly as if they had serious organic disease. A disorder of such uncertain pathogenesis, manifested by diverse symptoms which suggest organic disease, provides a challenging problem in differential diagnosis and leads to costly delays in the recognition of important organic lesions. It therefore seems important in the management of both functional and organic disease of the bowel to improve our understanding of the pathogenesis of the irritable colon.

Clinical observers of the irritable colon have long associated it with emotional tension. The patients often have a history of neurotic traits preceding the illness and reveal many of the signs of vasomotor instability. In many cases there are cleancut coincidences between difficult life situations and emotional conflicts and the colonic symptoms. Ten years ago White, Cobb and Jones[1] made an intensive psychologic study of these patients and demonstrated in a series of sixty cases how regularly these coincidences occur. For the last four years, in the Gastrointestinal Clinic of the New York Hospital, a small group of us have routinely taken personal histories on patients with irritable colon and have found few in which these coincidences do not exist.

Although the regular observation of a suspected factor in cases of a disease is a necessary step in establishing its role in etiology, the observation of coincidence is in itself inadequate. We therefore embarked four years ago on an experimental study of the irritable colon. In the laboratory we have attempted to isolate the emotionally charged life situation as a stimulus to colonic function, to separate it from the factors of diet, allergic sensitization, physical activity and intercurrent infection with which it is intermingled in ordinary living. If such a study is to be valid, the only acceptable experimental animal is man.

METHOD

Our experiments have been conducted on a series of healthy persons[2,3] and on patients with irritable colon.[4] The stimulus, the emotionally charged life situation, has been presented in the form of an interview on a matter known to be productive of emotional conflict in the subject of the experiment. In some of the "normal" subjects emotional conflict was produced by prolonged cold pain, with the hand in ice water or by painful compression of the head with a metal band.

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The changes in the function of the colon during the experiment have been followed in one of two ways. In some the lower sigmoid colon was observed continuously through a standard 25 cm. proctoscope, and the contractility and engorgement of the bowel were observed every

TABLE I
SCHEME FOR THE RECORDING OF CHANGES IN COLONIC FUNCTION

Grade	Contractile State	Engorgement
0	Lumen over 3 cm. wide, large haustrations	Thin, pale mucosa, with major veins of submucosa showing through
1+	Lumen 2–3 cm. wide, with smaller haustrations	Mild injection; smaller submucosal veins visible
2+	Lumen 1–2 cm. wide, with broad folds	Submucosal vessels obscured; diffuse pale pink mucosa
3+	Lumen occluded, but passable by manipulation	Medium rose color
4+	Lumen occluded and impassable	Bright red or purple

few minutes and recorded on arbitrary scales of zero to four plus activity. (Table I.) In most of the experiments the motility of the sigmoid was recorded kymographically, after passage of a latex balloon upward through the rectum. Although the wave patterns are complex and irregular, the total activity of the bowel at rest over periods as long as two hours is sufficiently constant to permit easy recognition of changes produced by experimental stimuli.

It has been, of course, impossible to devise simple objective criteria for the emotional state of the subjects during the experiments. Careful notes have been made of the attitude, facial expression, appearance of the skin, pattern of respiration and manner and content of talk of the subjects. From the sum of these observations we have estimated the depth and coloring of the subject's emotional response to the experimental situation. In many instances the subject has indicated the nature of his feelings by clear objective signs, such as weeping or cursing. In others the speech and behavior of the subject were significant of emotional tension only in the light of a thorough understanding of his personality and social history, an insight often gained several days or weeks later.

STUDIES ON HEALTHY PERSONS

Our initial studies were made upon a group of fifty healthy persons, including medical student volunteers and patients on the medical wards. All were in good general physical condition at the time of the experiments. In terms of their personalities all were "normals" in the gross sense, i.e., they had no overt manifestations of psychopathy, psychosis or perversion, and they had never been even slightly disabled by mental illness. None had had more than transient symptoms of colonic dysfunction at any time. The majority of these subjects responded to experimental stress in the laboratory with significant changes in colonic function, coincident with emotional tension. The following protocols will illustrate our findings:

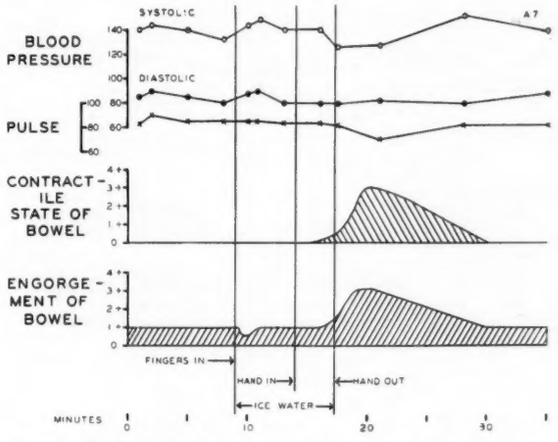

FIG. 1. Bodily changes accompanying resentment in reaction to cold pain.

Experiment 1. Proctoscopic observations were made on a subject whose right hand was immersed in ice water. (Fig. 1.) Shortly afterward he reported severe pain but in a calm and unruffled tone of voice. After eight minutes he suddenly became agitated and red-faced. He breathed heavily, cried out "This is torture" and removed his hand. Coincident with his outburst of temper, occlusive spasm and moderate engorgement were observed in the colon. These changes slowly subsided as the subject regained his composure. There was a close association in time between the colonic changes and the emotional outburst.

Experiment 2. A 22 year old medical student was observed proctoscopically for nearly two

hours. After a baseline period of fifty minutes a severe and sustained headache was produced by a metal head clamp. (Fig. 2.) This experience produced in him, according to his later description, an emotional conflict involving resentment of the investigators and self-reproach for having volunteered for the experiment. During the pain the motility and engorgement of his sigmoid colon were markedly increased and his blood pressure rose to a final level of 154/118. His skin was pale and sweating; he sighed frequently; he complained of nausea in waves that coincided with the observed increases in motility of the sigmoid. All of these changes subsided with the sudden end of the headache.

Experiment 3. A kymographic study was made upon a fifty-three year old tailor with hypertension. (Fig. 3.) It was already known that he was a hardworking, sensitive man who resented his station in life and had attempted to compensate for this by making sacrifices to give his son a college education. The son was ungrateful, a poor student and evidently destined to frustrate his father's desires. During the study of colonic motility his son's attitude was discussed and was interpreted as due to failure of the patient to exercise adequate discipline. During this time colonic motility was greatly increased. Following this interview the patient was quickly reassured by another and more sympathetic physician and the motility quickly returned to its former level. In three of seven such experiments on other subjects similar results were obtained.

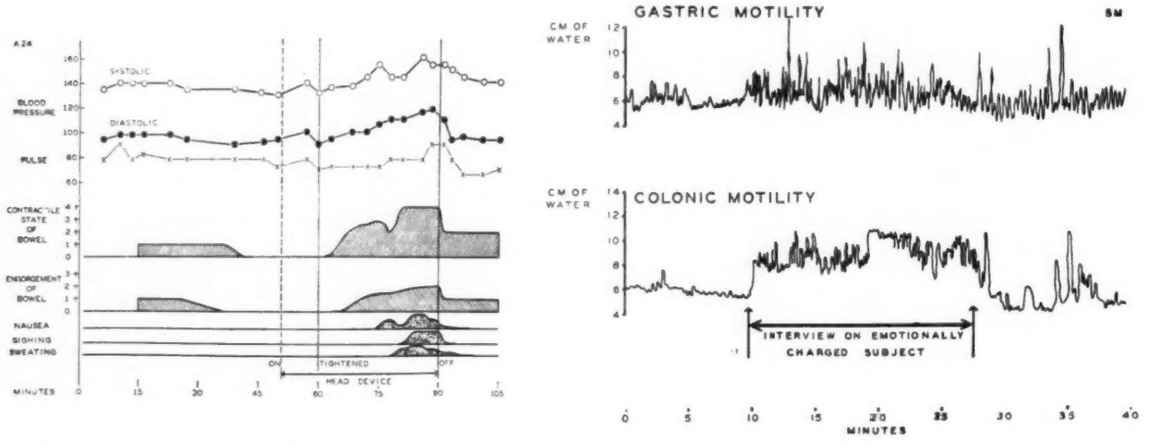

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FIG. 2. Bodily changes accompanying emotional conflict in response to experimental headache.
FIG. 3. Heightened colonic motility during unsympathetic interview in a patient with normal bowel function. The gastric motility tracing provides a control on the effects of respiratory changes and altered intra-abdominal pressure.

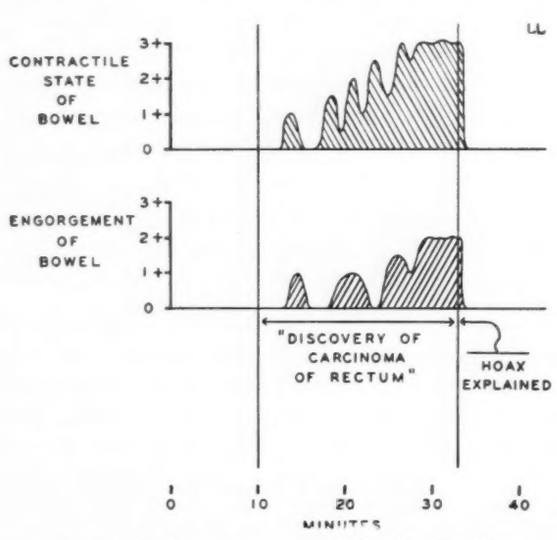


FIG. 4. Colonic changes accompanying baseless fear in a healthy subject.

Experiment 4. A twenty-two year old fourth-year medical student was asked to serve as a subject for an experiment which would require preliminary proctoscopy. After ten minutes of constant observation during which the bowel was completely relaxed and unengorged, the examiners commenced an elaborate hoax designed to make him believe that they had just seen a carcinoma of the rectum. (Fig. 4.) By various devices, including the signing of a biopsy permit and the taking of a fake biopsy, the tension was maintained over a period of twenty minutes. During this time occlusive spasm and moderate engorgement developed in the sigmoid. The subject's voice became thin and his speech no longer flippant. He asked for

our estimate of the operability of the lesion. Then we told him it was a hoax and thanked him for his cooperation. The colonic changes suddenly disappeared.

Comment. In our observations on healthy persons a variety of stress-producing experimental stimuli produced changes in motility and mucosal engorgement of the sigmoid colon similar to those seen in many cases of mucous colitis. These changes were seen only when an apparent emotional conflict was produced. The parallel emotional and colonic reactions could be evoked by the mere discussion of life situations which had produced stress in the past, or by the performance of certain painless maneuvers associated in the mind of the subject with cancer. On the other hand, it was possible for some to endure even prolonged and painful compression of the head with equanimity; and in these colonic changes did not appear. We infer from this that *special experience*, *conditioning* and *attitude* of the subject play a determining role in the development of colonic changes under stress.

OBSERVATIONS ON PATIENTS WITH IRRITABLE COLON

Using the same methods of observation we have studied nearly one hundred patients with irritable colon. In each of them a temporal coincidence had been noted between the episodes of intestinal symptoms and certain emotionally disturbing life situations. During each experiment one of these situations was discussed. In about two-thirds of the experiments the patient revealed by his speech and by his behavior that he was under emotional tension and simultaneously exhibited disturbances of colonic function. The changes in the colon have been of two types: the one an increase in the over-all activity of the sigmoid; the other a decrease in its activity. The following experiments will serve as examples:

Experiment 5. Proctoscopic observations were made on a thirty-seven year old German-born housewife with spastic constipation and essential hypertension. (Fig. 5.) For the first twenty-six minutes the patient remained relaxed and cheerful, despite the unusual circumstances, and the conversation involved knitting, her favorite leisure occupation. Her colon remained quiet except for a brief period when she bewailed her inability to bear children. She was then suddenly asked about the plight of her starving, bombed-out relatives in Germany. She was asked whether they had been Nazis. She appeared anxious and defensive; her blood pressure rose; the lumen of her colon became occluded and its mucosa markedly engorged. When she was comforted and reassured, these changes subsided. They recurred when she spontaneously expressed resentment toward her husband because he was able to have normal bowel movements.

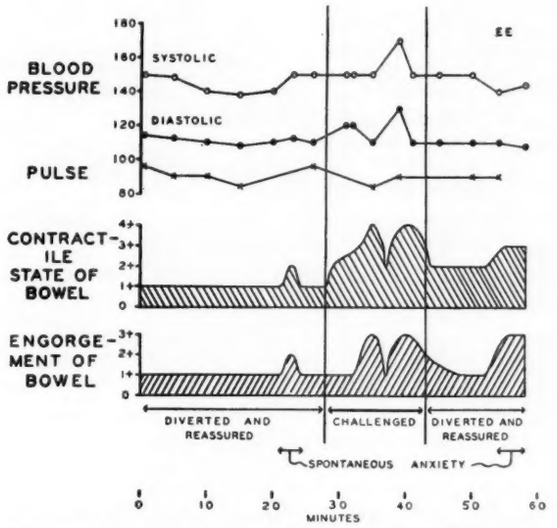
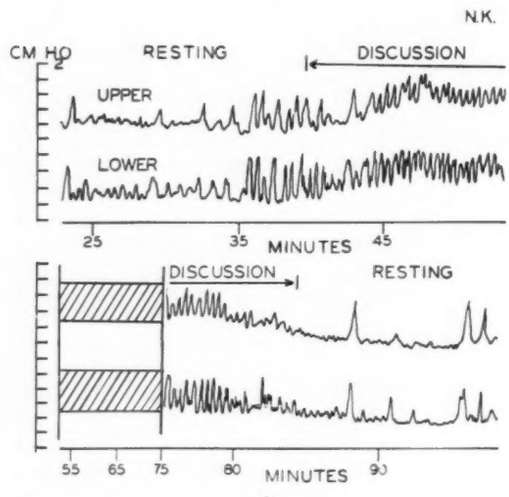


FIG. 5. Thirty-seven year old housewife with spastic constipation. Increased activity of sigmoid accompanying emotional conflict (continuous proctoscopic observation).

Experiment 6. A sixty-two year old spinster, a domestic servant, had been constipated for about fifty years. In the past twenty-four years this had been interrupted by brief periods of violent diarrhea. Because of an alcoholic stepfather she had been separated from her mother at the age of thirteen and raised by foster parents. Her foster mother was rigid and dominating and effectively blocked her efforts to achieve independence. When the foster mother died the patient was already thirty-eight but felt inadequate to deal with her problems. At this time she had the first of many attacks of diarrhea which occurred when, in trying to adapt herself to her environment, she felt lonely and helpless.

A kymographic study was made on this patient. (Fig. 6.) During an interview the patient spoke quietly but under pressure, and expressed hostility toward her foster mother and other persons who had been unreasonable toward her. She defended the righteousness of her own behavior at every turn. At no time did she weep or give any other expression to the feelings of futility which she had mentioned in earlier interviews. During the entire interview the tone and wave-like contractions of her sigmoid colon were increased. These returned to a lower level when the physician left.



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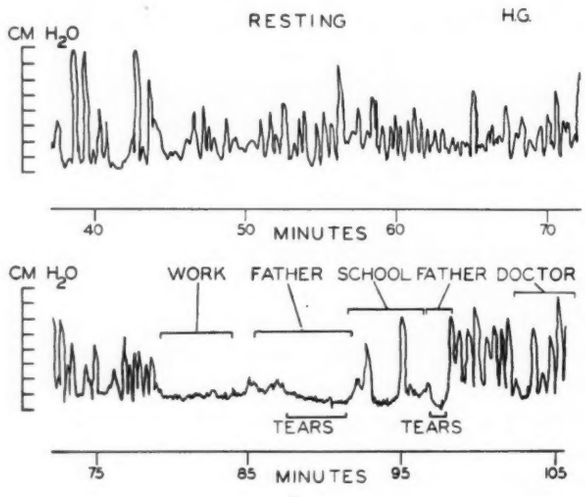

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FIG. 6. Sixty-two year old domestic servant with constipation interrupted by brief periods of diarrhea. Heightened motility of the sigmoid which coincided with discussion of life stresses. The shaded area indicates the range of intraluminal pressures during that part of the tracing which is not reproduced. The sustained excitation of the bowel is apparent.

FIG. 7. Nineteen year old unemployed male with diarrhea for three and one-half years; reduction in motility of sigmoid during unsympathetic discussion of life problems.

Experiment 7. A nineteen year old unemployed boy had suffered from diarrhea for three and a half years. He was the only child of a Protestant father and a Catholic mother. His mother had been married before and had a daughter by that marriage, fifteen years older. The boy had been specially attached to his father and had often gone on trips with him. He had done poorly in school and had frequently been depressed on Sunday afternoons because of the prospect of returning to school. The diarrhea had begun during the terminal illness of his father and at a time when he was failing conspicuously in school. The bowel movements had been most frequent when he left his home to look for work or to come to the clinic. A sigmoid motility study (Fig. 7) revealed a pattern of regularly recurring contractions, most of them of large size. During this period the patient rested undisturbed on the laboratory bed. Then a physician began to discuss with him unsympathetically several of the distressing features of his life—his unemployment, his father's death and the diarrhea itself. In each instance it was suggested that his own behavior was not praiseworthy. During this time he spoke in a low voice about his grief over his father, his fear of embarrassment through being incontinent of feces and his feelings of inferiority. The major wave-like movements completely disappeared from the motility tracing. They reappeared briefly in association with a flare of resentment over the way his teachers had handled him at school. They disappeared again when the subject of his father's death was reintroduced and when it was suggested that his clinic physician was no longer interested in seeing him. On two of these occasions he burst into tears.

In some experiments the patterns of increased motility and of decreased motility have occurred successively and have been correlated with changes in the mood and general behavior of the subject.

Experiment 8. A forty-seven year old twice-married housewife complained of constipation for thirty years, interrupted in the past five

years by frequent episodes of severe diarrhea. Her mother had died when the patient was five and a stepmother had been cold to her. Uninstructed in problems of sexual adjustment, she eloped at the age of seventeen and in the next year went through an unwanted pregnancy. Her constipation began at this time and continued through a decade of childbearing, the death of her first husband and her adjustment to a second husband and two hostile stepdaughters. The only person who gave her unqualified devotion was her eldest son and she had come to depend on him for encouragement and for the solution of practical problems. When she was forty-two her son died suddenly in military service. Within two hours of the receipt of this news she developed severe diarrhea, which recurred over the succeeding five years whenever she felt inadequate to cope with her problems.

The motility of the sigmoid colon was recorded in this patient during an interview in which many of the above events were discussed. (Fig. 8.) At first she spoke of her father, whom she admired, with an air of serenity and pride. Subsequently she twice discussed the hostile behavior of her stepdaughters. On the former occasion she appeared downcast, almost motionless and wept freely; this was accompanied by a reduction in tone and in wave-like motility of the colon. On the latter occasion the form of the discussion brought out her own hostile feelings and her eyes were dry, her respirations quick and deep, her voice clear and animated; this time the tone and wave-like contractions of the colon were heightened. During the rest of the interview, on four separate occasions, there was a reduction of motility of the sigmoid colon associated with weeping. The shortest of these periods was one minute in length. Two of these episodes were associated with a description of the death of her son and of his funeral, events which had coincided with the onset of her phase of severe diarrhea.

Comment. In patients with irritable colon, as with healthy persons, disturbances of the motility of the sigmoid colon occur quite regularly in association with emotional conflict. This conflict has appeared to lie between feelings of hostility and resentment and feelings of guilt and self-reproach, and hence does not differ materially from the emotional states which accompany other psychosomatic phenomena.

There has likewise been no significant difference between the emotional *conflicts* associated with increased sigmoid motility and those associated with decreased motility. There was, however, a notable difference in the *dominant moods* and *behavior patterns* associated with these colonic changes. Patients who spoke of their emotional problems in a hostile, defensive, spirited manner, with a tense voice and a dry eye, exhibited an increase in sigmoid motility. Those whose statements betrayed attitudes of helplessness and defeat, whose voices were subdued, showed a reduction in sigmoid motility, often corresponding exactly with periods of weeping.

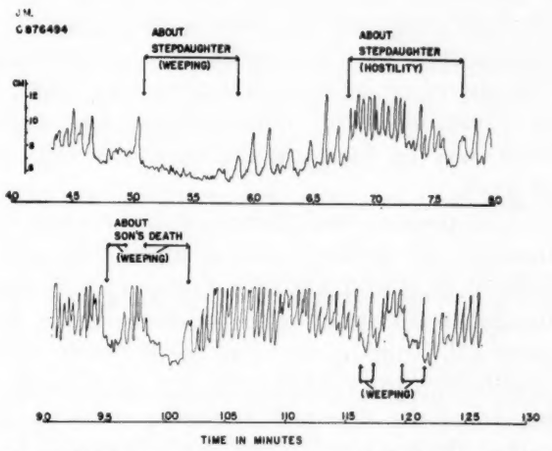

FIG. 8. Forty-seven year old housewife with alternating constipation and diarrhea for thirty years. Tracing shows periods of excitation and periods of depression of sigmoid motility, correlated with changes in emotional state.

OBSERVATIONS

Some patients with irritable colon are troubled with constipation, others with diarrhea; still others have experienced both symptoms in successive periods. It is natural to inquire how these alterations in colonic function, seen in the laboratory, may be related to the mechanisms of constipation and diarrhea.

Clinically, the patient with spastic constipation is usually tense, with ill-concealed hostility and with an air of rigid determination to solve his problems. On physical and

roentgenologic examination there is often a dilated, hypomotile, gas-filled proximal colon; yet on proctoscopy the lumen of the sigmoid is often occluded by spasm. In the laboratory he usually expresses his hostility and simultaneously exhibits increased wave-like motility of the sigmoid. Prolonged study of these contractions with tandem balloons shows most of them to be non-propulsive. We therefore believe that these are spastic or "holding-back" contractions, and that they may be fundamental to the retention of feces.

The patient with functional diarrhea is usually soft spoken, with a superficial attitude of guilt and a countercurrent of deeply buried resentment and with a sense of personal inadequacy to deal with his problems. On proctoscopic examination the lumen of the sigmoid is usually wide open rather than occluded. In the laboratory he expresses feelings of hopelessness, most eloquently by weeping, correlated with reduced wave-like motility in the sigmoid. We believe that this abolition of wave-like contractions helps to establish, in the words of Alvarez,[5] a heightened gradient of motility between proximal and distal colon, permitting the ready passage of feces.

The numerous patients with alternating constipation and diarrhea often show clinically a remarkable fluctuation in their moods. Occasionally, as in the last patient described, these mood changes occur with sufficient rapidity to be detected in the course of a single experiment. The episodes of constipation and diarrhea seem to be related in some manner to alternate feelings of aggressive self-confidence and personal inadequacy to deal with the environment.

These observations demand a change in our concepts of the *treatment* of irritable colon. We have long thought of this as a disorder inherent in the colon; yet there is clinical and experimental evidence to indicate that the colonic changes are merely a part of a total emotional and bodily reaction to environmental threats. The colonic disorder is apparently a normal accompaniment of emotional tension, like blushing of the face, and the philosophy of its treatment may be clarified by the use of the same analogy. If a woman should blush when an off-color story is told, it would seem illogical to apply medicaments to the skin or to interfere with vasomotor functions in the skin. Since the cause for the blushing is recognized, treatment of the end organ would be abandoned and the "patient" would be advised to shun the company of those who tell off-color stories or else to learn to be more tolerant of such uncouth behavior. In more general terms, which I think apply also to irritable colon, either the patient's environment must be changed, or his attitude toward it must be changed, or both. Simple psychotherapy heads our list of therapeutic measures. We have come to consider diets and drugs as auxiliary measures which, when used alone, will not be adequate to produce relief.

Although we may grant that the usual primary cause of the irritable colon is environmental stress productive of emotional tension, recognition of this does not regularly provide relief for the patient. Most patients can profit further from the leisurely and subtle exploitation of the physician-patient relationship. It would greatly reinforce this bond if we possessed truly potent therapeutic agents, capable of modifying the disturbed activity of the colon. Such agents could fulfill the roles occupied by alkalies in the management of peptic ulcer and by antithyroid agents in the treatment of Graves' disease.

The search for such agents has heretofore been conducted chiefly by experiments on the isolated smooth muscle of experimental animals and by clinical trial in man. When tested upon the human small intestine by the use of the Miller-Abbott tube, no one of these "antispasmodics" has been shown to be both effective and practical. We believe these agents should be tested for their capacity to modify the kymographic patterns of disturbed sigmoid motility described above. These patterns appear to be a measurable index of the actual clinical disorder. Furthermore, the study of effects

on the small intestine alone may be subject to error in that the responses of the small intestine and the distal colon to the same drug may be not even qualitatively similar.[6] The sigmoid balloon is better tolerated than is the Miller-Abbott tube and hence many artefacts due to the discomfort of the patient may be eliminated. Our search for "antispasmodics" along these lines has already begun and two extremely potent though impractical agents have been identified.

SUMMARY

When under stress induced by experimental stimuli, both healthy persons and patients with irritable colon may show disturbances in motility and engorgement of the sigmoid colon coincident with periods of emotional tension. Two patterns of altered sigmoid motility have been recognized: the one an increase in tone and/or wave-like contractions associated with overt moods of hostility and aggression; the other a decrease in tone and/or contractions associated with overt behavior symbolizing hopelessness and defeat. A possible relationship of these patterns to the mechanisms of spastic constipation and functional diarrhea is discussed.

CONCLUSION

Clinical symptoms of the disorder, irritable colon, are regularly associated with emotionally charged life situations. When such situations are created in the laboratory, certain of the objective phenomena of the disorder are reproduced. We therefore conclude that in most instances irritable colon is a bodily change accompanying emotional conflict in response to environmental stress.

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Review

Use and Abuse of Thiouracil Drugs*

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SINCE Astwood in 1943 introduced the thiouracil drugs in the treatment of hyperthyroidism, attention has been focused principally on the results achieved and on the toxic manifestations of the drugs used. At the present time such antithyroid therapy is in more general use, and an inquiry into its abuse should be both enlightening and profitable. A recent experience with agranulocytosis from propylthiouracil emphasized the need for pointing out the pitfalls of such therapy.

A thirty-nine year old housewife consulted us on November 4, 1948, for treatment of hyperthyroidism not relieved by previous treatment. Her symptoms began six months before she came to the clinic. Her initial basal metabolic rate was +64. Treatment consisted of one pill (50 mg.) of propylthiouracil a day for the preceding three and a half months. Two days prior to admission to the clinic a sore throat developed and she stopped the medication herself.

Examination revealed that the patient was acutely ill, with a temperature of 102°F, severe tonsillitis and pharyngitis, a bilaterally enlarged thyroid gland and moderately severe hyperthyroidism. An immediate leukocyte count showed 4,200 leukocytes and 1 per cent neutrophils. A diagnosis of severe primary hyperthyroidism and agranulocytosis secondary to propylthiouracil was made and she was admitted at once to the hospital. Treatment with penicillin and streptomycin produced a prompt response in the fever and sore throat and a gradual return of the leukocytes to normal levels during the ensuing week. (Fig. 1.)

Following recovery from the agranulocytosis the basal metabolic rate was +36 and on clinical grounds alone further preoperative preparation was deemed necessary before thyroid surgery could be done. A test dose of 50 mg. of methylthiouracil was well tolerated and she was therefore given methylthiouracil for forty-nine days in a dose of 200 mg. daily. Lugol's solution was added during the last twenty-one days. The metabolic rate fell to +15 and she then underwent subtotal thyroidectomy, with removal of 75 gm. of tissue. Since operation she has remained well and free of symptoms, with normal basal metabolic rates.

In summary, this patient represents a perfect example of the misuse of propylthiouracil. (Fig. 2.) She had severe hyperthyroidism which was treated with only 50 mg. of propylthiouracil daily for three and a half months. This dose was entirely too small to control her symptoms and it finally led to the development of agranulocytosis while at the same time leaving her still in a state of moderate thyrotoxicosis. Fortunately, she tolerated methylthiouracil so that she could be fully prepared for subtotal thyroidectomy and relief of her disease.

Among the first 1,000 patients with hyperthyroidism treated at the clinic since the introduction of the thiouracil drugs there were fifty-six patients who had received one of these agents at some time prior to our initial examination. Analysis of the records of these patients serves as the basis for determining how these drugs are being used by physicians in various communities. These fifty-six patients fall into six different groups according to the pattern of their treatment.

Group I. *Referred for Thyroid Surgery:* There were fifteen patients properly diagnosed as having hyperthyroidism, started on preoperative preparation and referred to us for surgery. Antithyroid medication had been taken for from four days to seven

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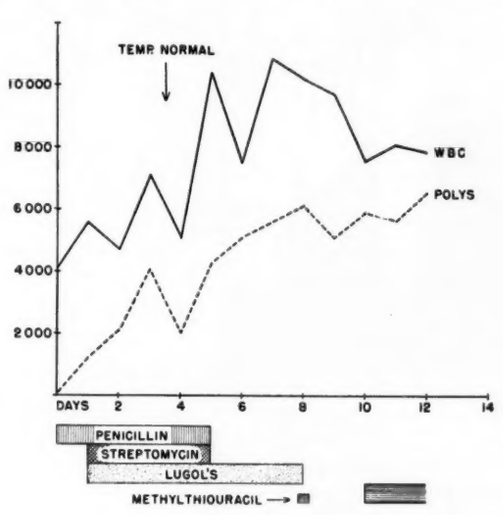
weeks. Most of these patients were partially relieved of their hyperthyroidism and needed more treatment before operation. Five of them had normal basal metabolic rates, and all five needed two to three weeks of iodine therapy before surgery was advisable.

the basal metabolic rate to normal. Granting the possibility that some of these patients might have obtained prolonged remission of their hyperthyroidism by adequate medical treatment, the chances of obtaining remission were remote as long as some toxicity



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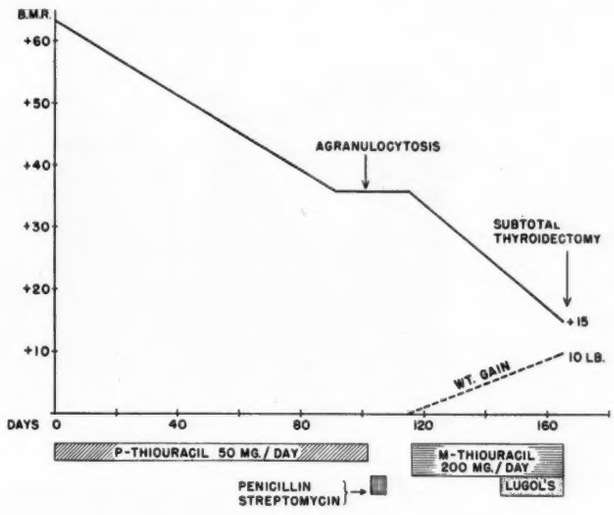

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FIG. 1. Agranulocytosis from propylthiouracil.
FIG. 2. Primary hyperthyroidism developing agranulocytosis to propylthiouracil.

Group II. *Failure of Medical Treatment to Relieve Fully:* There were fifteen patients who received thiouracil or propylthiouracil for variable periods of time as a form of medical treatment but sought further care because of persistence of symptoms. The methods of treatment varied widely. There was no uniformity in dosage of drug used or length of treatment. Thiouracil or its derivatives was used either alone or in combination with iodine and either continuously or intermittently. Roentgen radiation to the thyroid had been tried in several. Treatment of one patient covered a period of nine years. (Fig. 3.) In other patients treatment was carried out for as short as six weeks. The basal metabolic rates at the time of their first clinic visit ranged from +2 to +50, average +27. All patients needed further preoperative preparation before operation could be done because of the presence of some degree of hyperthyroidism.

Every patient in this group had spent considerable time under medical treatment which failed to relieve symptoms and restore persisted. The average basal metabolic rate of +27 for the entire group indicates that full control of the thyrotoxic state had not been achieved. Failure to appreciate this by the physician was responsible for many of the poor results with antithyroid drugs.

The size of the goiter has an important bearing on the final results of medical treatment of hyperthyroidism. As a general rule the smaller the goiter the greater is the chance of producing a remission by medical treatment alone. In fourteen of the fifteen patients in whom the surgical specimen was weighed the amount of tissue removed varied from 10 to 210 gm. Seven patients had 40 gm. or more (average 93 gm.) of tissue removed, indicative of a large goiter. They, therefore, could have been considered as poor candidates for medical therapy alone. The other seven patients had small goiters as evidenced by surgical specimens weighing 34 gm. or less (average 19 gm.). It is notable that prolonged medical treatment in these patients with small goiters failed to produce relief of hyperthyroidism.

This failure to control hyperthyroidism in these latter seven patients is undoubtedly due to inadequate doses of thiouracil drugs.

Group III. *Relapse or Recurrence of Hyperthyroidism Following a Medically Induced Remission:* This group consisted of thirteen patients who had received thiouracil or propylthiouracil long enough to have obtained remission of their thyrotoxicosis. They came to the clinic because of recurrence of hyperthyroidism and need for further treatment. Duration of previous therapy ranged from three months to twenty months, average 7.4 months.

The duration of the remission was short in most cases. Two patients had a relapse while on maintenance therapy—one while on iodine and the other while taking 100 mg. of propylthiouracil a day. Eight patients experienced a relapse of hyperthyroidism within the first three months after stopping treatment. One patient had a recurrence of toxicity five months after stopping therapy. The two remaining patients received 150 mg. of propylthiouracil daily for only three months and had remissions lasting one year and one and a half years, respectively, at which time the hyperthyroidism returned. The patient receiving the longest course of treatment (thiouracil for twenty months) had a relapse of hyperthyroidism within two months after stopping the drug.

Maintaining the basal metabolic rate at minus levels throughout medical treatment is said to be important in inducing prolonged remission. Information in our records covering the basal metabolic rates during the previous treatment unfortunately is incomplete. Of note, however, was the occurrence of basal metabolic rates below zero in three patients during their course of medical treatment. One patient whose basal metabolic rate fell from +30 to −10 during six months of propylthiouracil therapy had a relapse of hyperthyroidism within five weeks after stopping the drug. The other two patients had metabolic rates as low as −3, and both had a return of hyperthyroidism within three months after stopping treatment.

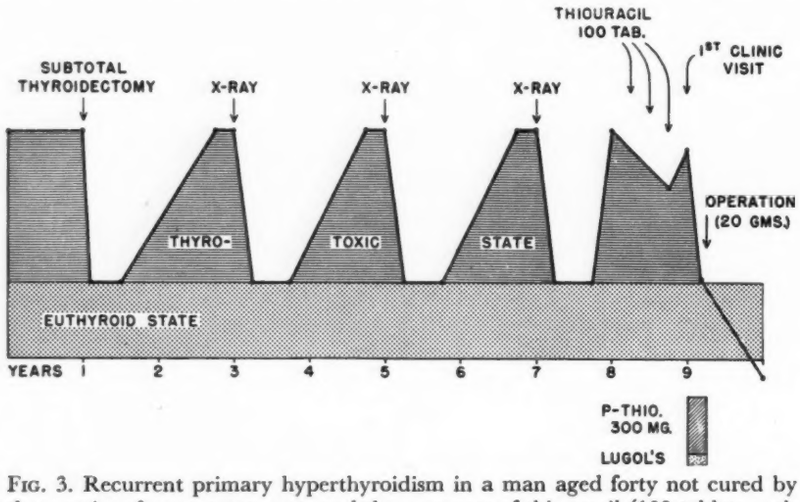

FIG. 3. Recurrent primary hyperthyroidism in a man aged forty not cured by three series of x-ray treatments and three courses of thiouracil (100 tablets each course).

Five patients of Group III had had thyroid surgery in the past followed by recurrent thyrotoxicosis which was treated medically. In each case there was prompt recurrence of hyperthyroidism upon cessation of antithyroid medication. One of these patients had persistent thyrotoxicosis inasmuch as during her first operative procedure only a hemithyroidectomy had been performed because of moderately severe reaction during operation. In any event all five of these patients represent failures of both medical and previous surgical treatment.

The size of the goiter in each of the groups was estimated from the amount of tissue

removed at operation. In ten of the patients the surgical specimen weighed 20 to 150 gm., average 49 gm. The patient with persistent hyperthyroidism required only a right subtotal hemithyroidectomy with the removal of 29 gm. of tissue. These figures indicate that most of these patients had large goiters and for that reason alone were poor subjects for prolonged medical treatment.

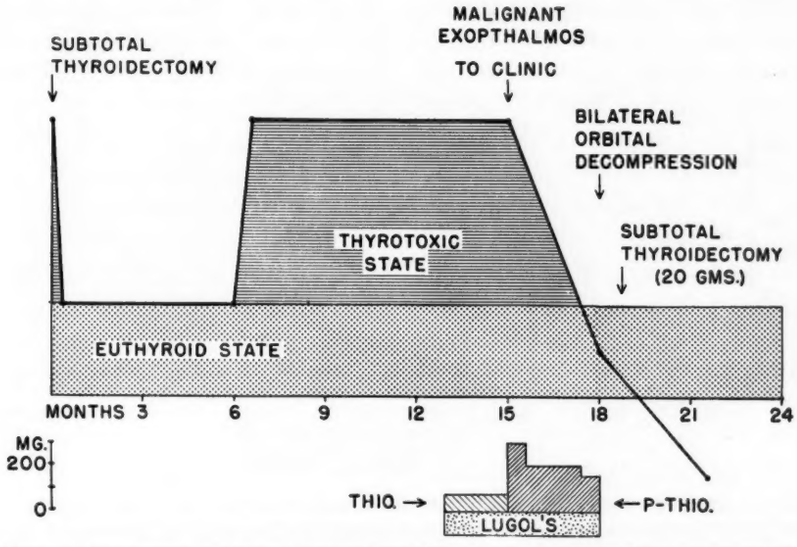

FIG. 4. Recurrent primary hyperthyroidism with exophthalmos progressing while patient (woman, aged thirty-nine) was on inadequate antithyroid treatment.

One male patient had a multiple colloid adenomatous goiter. The surgical specimen weighed 150 gm. Enlargement of the gland had occurred during medical treatment. This patient was doomed to probable failure with medical treatment on three points, namely, the goiter was nodular, it was large to start with and became enlarged during treatment. Recognition of these factors, particularly that the goiter was large and nodular, should have directed this patient into surgical channels at once, thereby saving him both the time and expense of futile medical treatment.

Group IV. *Complications During Medical Treatment:* This group consisted of nine patients referred to the clinic for surgical treatment because of the development of some complication during their previous medical treatment. Five of these patients had had a depression of the total leukocyte count, four from thiouracil and one from propylthiouracil. In each case additional treatment with propylthiouracil was accomplished before operation was done, without the development of agranulocytosis. The depression of the leukocyte count had been mild in each case and the neutrophils usually remained above 45 per cent. It is nonetheless desirable for the physician to discontinue antithyroid drugs in any patient whose total white count falls below 4,500 and neutrophils below 40 to 45 per cent until at least a recheck has been made to eliminate laboratory error. Continuation of antithyroid drugs in the presence of counts below these levels may be undertaken only if absolutely necessary for the control of thyrotoxicosis and then only under very close supervision with all necessary facilities available for the energetic treatment of agranulocytosis, should it occur.

Generalized skin rash was responsible for the discontinuance of medical treatment in two patients. One of these patients was sensitive to propylthiouracil and a similar skin rash developed after ten days of treatment with methylthiouracil.

Treatment was discontinued in one patient after six months of propylthiouracil therapy when fever developed, erroneously

interpreted as drug fever. She later tolerated thirty days of preoperative treatment with a daily dose of 200 mg. of the same drug. Drug fever usually occurs during the first three weeks of treatment and rarely if ever appears after six months of continuous therapy.

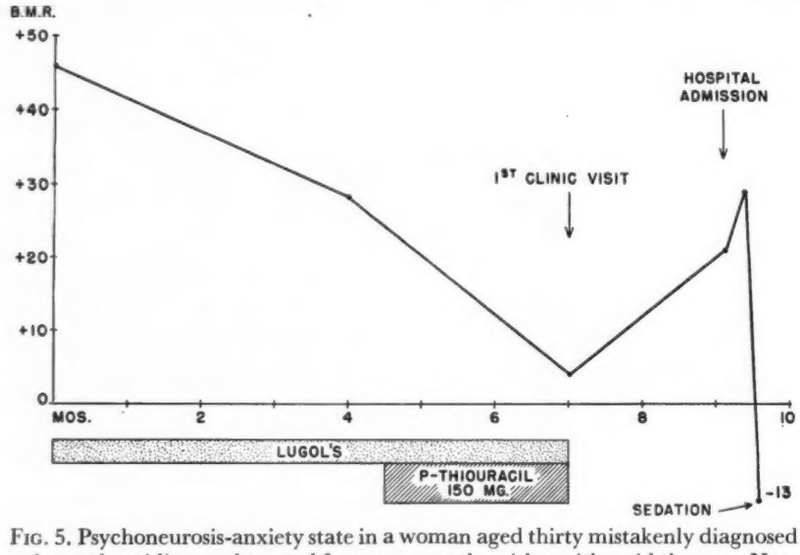

FIG. 5. Psychoneurosis-anxiety state in a woman aged thirty mistakenly diagnosed as hyperthyroidism and treated for seven months with antithyroid therapy. Note the fall in the basal metabolic rate under sedation.

Another patient was referred to the clinic for surgery because of rapid progression of exophthalmos while she was on medical therapy. (Fig. 4.) The treatment consisted of 75 mg. of thiourea and ten drops of Lugol's solution daily for the previous seven weeks. When the patient was first seen at the clinic her metabolic rate was +27, indicating the existence of a moderate degree of hyperthyroidism. Although the exophthalmos might have progressed in spite of any form of therapy, it was nevertheless important to control the hyperthyroidism which was not accomplished in this patient with the treatment she was receiving. Early control of hyperthyroidism should always be attempted for it seems likely that as long as moderately severe thyrotoxicosis persists there is little chance for any improvement in exophthalmos. When we first saw this patient, her eyes were a greater problem than the hyperthyroidism and bilateral orbital decompression was performed as soon as her hyperthyroidism was sufficiently controlled to permit operation. Subtotal thyroidectomy was done two weeks later.

Group v. *Medical Treatment not Indicated:* Prolonged medical treatment was given to two patients with large intrathoracic goiters, one of which weighed 275 gm. and the other 90 gm. One patient was treated with thiouracil for two years. The point here obviously is that prolonged medical treatment is contraindicated in this type of toxic goiter.

One patient was treated a long time with thiouracil but cooperated so poorly that operation was recommended. Another patient cooperated well for nine months of continuous medical treatment but then sought surgical aid because of discouragement over the necessity for continued medical supervision. It is possible that more and more patients may fall into this group, particularly if repeated courses of thiouracil drugs are found necessary to control relapses.

Group VI. *Mistaken Diagnoses:* None of the fifty-six patients discussed fall into this group, but we have recently seen some examples. The most frequent error in diagnosis is mistaking anxiety neurosis for hyperthyroidism. We have seen a patient with an anxiety neurosis, mistakenly diagnosed as

hyperthyroidism, who received antithyroid treatment for seven months. (Fig. 5.) Unquestionably there may be difficulty occasionally in distinguishing between the two conditions and all possible aids in diagnosis may be necessary in order to settle the point. Basal metabolic rates done under pentothal® anesthesia as suggested by Bartels[1] have been helpful. A therapeutic trial with iodine or with propylthiouracil may also be given. However, a therapeutic trial with propylthiouracil should be limited to six or eight weeks, except for the occasional patient with adenomatous goiter in whom three months may be needed for full response. If a response is not sufficiently clear-cut by the end of this period, it is unlikely that longer treatment will make much difference.

SELECTION OF THIOURACIL DRUGS

Current concepts of the use of the thiouracil drugs are clearer than they were two or three years ago. In this country propylthiouracil is certainly the drug of choice. Methylthiouracil is slightly more active but is also capable of producing a higher percentage of toxic reactions. Thiobarbital has been abandoned because of its prohibitive toxicity (28 per cent) and thiouracil, with 10 per cent toxic reactions, is reserved for use under close supervision only in those patients who are intolerant to propylthiouracil and methylthiouracil. Thiouracil in preference to the others has also been recommended in the treatment of thyroiditis.

PREOPERATIVE THERAPY

The preoperative use of propylthiouracil as a method of preparing toxic thyroid patients for surgery is now well established and universally accepted. The dosage of propylthiouracil is 200 to 300 mg. a day. The higher dose is used in all cases of adenomatous goiters with hyperthyroidism and all cases of primary hyperthyroidism with large glands or glands previously saturated with iodine. Occasionally a dosage of 400 mg. daily is used when the response to treatment is unusually slow.

The duration of treatment is governed by the height of the metabolic rate, the clinical response and the presence of coincidental debilitating diseases. In patients with uncomplicated primary hyperthyroidism treatment is given for as many days as the basal metabolic rate is elevated above normal. If clinical response is slowed by previous iodine therapy, an additional two or three weeks is allowed. Patients with adenomatous goiters are treated for twice as many days as the basal metabolic rate is elevated above normal. Additional time is allowed for patients who previously received iodine.

Lugol's solution is used for its involuting effect on the gland in patients with primary hyperthyroidism only. The dosage is ten drops once a day. It is used only during the last three weeks of propylthiouracil therapy except for those patients who are severely toxic and critically ill; in the latter it is used also during the first two weeks of treatment. This program permits early and rapid amelioration of symptoms and removes the danger of a thyroid crisis which may occur before the slower acting propylthiouracil has had a chance to exert its effect. Iodine is not used in adenomatous goiters since surgical difficulties are not increased by the use of propylthiouracil alone in such glands. Whenever there is doubt as to whether the gland is a primary hyperplastic goiter or an adenomatous goiter, it is wiser to administer Lugol's solution during the last three weeks of therapy.

Toxic reactions to propylthiouracil have occurred consistently in about 2 per cent. At the Lahey Clinic we have had twenty-two reactions in 1,130 cases. The minor reactions include skin rash, urticaria, mild depression of the total leukocyte count, total neutrophil count or both and arthralgia with joint effusion. Two patients had drug fever, necessitating abandonment of further use of the drug. There have been seven cases of agranulocytosis with no deaths. Livingston and Livingston,[2] Eisenmenger and Steele,[3] Bartels,[4] and Juliar and Harris[5] have reported instances of agranulocytosis due to propylthiouracil. In the most recent

report by Juliar and Harris the patient died and, although they attributed the death to propylthiouracil, the issue was clouded by the occurrence of a severe reaction to a blood transfusion. It is clear, nevertheless, that agranulocytosis is one of the possible toxic effects of propylthiouracil and for this reason alone careful supervision of all patients who take the drug is necessary.

The guiding principle in the preoperative use of thiouracil drugs is full and complete control of hyperthyroidism before thyroidectomy is attempted. Partial control is not enough. Iodine alone accomplishes partial control and, although surgical results with iodine preparation were satisfactory, the improved surgical results possible with the thiouracil preparations are the objective of this form of treatment. Aids to determining when hyperthyroidism is completely controlled include the following: gain in weight, loss of all symptoms, a basal metabolic rate around zero and a pulse rate below 90. The rapid pulse rate is usually the last objective sign to disappear with therapy and it is the first adverse sign to appear during operation. When all these conditions are met, the patient may usually be considered to be ready for surgery. When any one of these factors is lacking, it is a matter of judgment as to whether the patient should be operated upon.

Overtreatment is to be avoided because of the surgical difficulties which arise in the presence of myxedema in primary hyperthyroidism. Excessive respiratory depression from morphine sensitivity and excessive edema of the tissues of the neck, including the vocal cords, are the major complications. Basal metabolic rates below zero and elevated blood cholesterol levels are indications for withholding surgery until they have been restored to normal. In our experience we have not produced myxedema in any patient with adenomatous goiter regardless of how high the dose or how long the preoperative treatment.

The thyroid patient who has been properly prepared for surgery should go through the operation with minimal rise in pulse and pulse pressure, and the postoperative convalescence should be smooth and uneventful. It is the meticulous attention to details of preparation plus skillful anesthesia and surgery which produces the best results in this method of handling patients with hyperthyroidism.

THIOURACIL TREATMENT OF HYPERTHYROIDISM

Prolonged administration of thiouracil drugs as a form of medical treatment for hyperthyroidism has not been in use long enough to settle many of the problems that have arisen. Even at the present time there is no uniformity in the selection of cases, size of dosage, duration of treatment or contraindications. Some of these questions must remain unanswered for a long time but from the experience gained in the past six years certain facts now appear to be established.

1. Full control of the hyperthyroidism during the entire period of medical treatment is an absolute necessity for the production of remission. It is illogical to expect remission if a low grade hyperthyroidism is allowed to persist during treatment. In general, it would be better to err on the side of overtreatment than undertreatment. Poate[6] and others[7,8] recommended that patients be maintained in a state of mild hypothyroidism throughout treatment since this factor leads to a higher percentage of prolonged remissions. It is not clear at this time whether it is the presence of myxedema or merely the complete control of hyperthyroidism that is important in producing remission of the disease. In any case the aim of prolonged medical therapy should be to depress the basal metabolic rate to zero or slightly lower and to maintain it at that level throughout the duration of treatment. If this rule were to be followed more consistently, medical treatment might possibly be more effective.

2. Toxic reactions to propylthiouracil occur in 2 per cent of patients and in 0.6 per cent of patients agranulocytosis may be expected to develop. Prolonged treatment, therefore, should not be undertaken unless the patient will continue under supervision

and unless facilities are available for the proper management of adverse reactions. Promiscuous use of the thiouracil drugs is certain to lead to such reactions and possible fatalities.

3. The type of hyperthyroidism most likely to respond to medical treatment is primary hyperthyroidism or Graves' disease, with small glands and mild toxicity.[9] Prolonged remissions have occurred more often in this type than in all others. The duration of such remissions is still uncertain. The results of medical treatment in patients with large goiters and severe toxicity are less satisfactory.

4. Contraindications to prolonged medical treatment include intrathoracic goiter, tracheal compression, toxicity to thiouracil drugs, solitary adenoma and uncooperative patients. The first three of these contraindications are obvious. The patient with solitary adenoma should be given surgical treatment because of the high incidence (11 per cent or more) of carcinoma in this group. Carcinoma may also occur in primary hyperthyroidism and in adenomatous goiters although the incidence is much less than it is in the solitary adenoma. It is certain that widespread use of medical treatment will eventually witness the occurrence of carcinoma of the thyroid in a small number of patients receiving prolonged medical therapy.

Some patients are unsuitable for prolonged medical treatment because of their unreliability in all matters, their discouragement over failure to be cured or their psychologic resentment over the necessity of prolonged medical supervision. Others object to the cosmetic disfigurement of a large goiter. In such patients operation is the treatment of choice.

The foregoing discussion covers the features of prolonged medical treatment which seem to be accepted by most investigators of the subject and can be considered as established opinions to date. On the other hand, there is an additional group of unknowns which still remain to be settled.

1. The duration of medical treatment so far has been a matter of arbitrary decision on the part of the men who have been studying these drugs. The general consensus is that treatment must be prolonged if remissions are to be permanent.[10] Length of treatment has varied from three months to two years. We have witnessed patients who have had continuous treatment for two years and have relapsed immediately on stopping the drug. Also, patients have had a remission lasting up to three years after no more than three months of treatment. It is possible that proper selection of patients and complete control of the thyrotoxicosis will be more vital than actual duration of treatment.

2. Patients with adenomatous goiters are probably not suitable for medical treatment.[11–13] The natural course of adenomatous goiter with hyperthyroidism is one of steady progression without spontaneous remissions and of progressive enlargement of the gland. It is possible to control the hyperthyroidism with constant thiouracil treatment, but the chances of producing a lasting remission not requiring further treatment are certainly less than with primary hyperthyroidism. In some patients, nevertheless, such an apparent abatement of hyperthyroidism has been accomplished so that these successes cast some doubt on the question of just what form treatment should take.[14,15]

3. Recurrent primary hyperthyroidism following operation presents a similar problem. Assuming that the surgical technic was correct at the time of the subtotal thyroidectomy, recurrence of hyperthyroidism implies that the original stimulus to the development of thyroid toxicity is still strong enough to override the effects of surgery. It is true that some recurrences are mild enough to be fully controlled by iodine therapy alone. These individuals can be controlled by any antithyroid therapy. On the other hand, in a number of patients recurrent thyrotoxicosis is quite severe and it is in this group that differences of opinion exist as to proper treatment. Some authors[8,16,17] recommend only medical treat-

ment because of the greater risk of producing recurrent laryngeal paralysis or chronic parathyroid tetany with further surgery. Others[18] recommend surgery because of the failure of prolonged medical treatment to effect a cure. Suitable studies will be necessary to clarify this question. Radioactive iodine may eventually prove to be the preferred type of treatment.

4. The late effects of prolonged thiouracil therapy on the thyroid gland are still unknown. The questions of disappearance of the goiter[19] or development of malignant changes in the gland can be answered only after further observations covering these points.

SUMMARY

An appraisal of the current status of the thiouracil derivatives in the treatment of hyperthyroidism has been attempted, based upon an analysis of the records of fifty-six patients referred for surgery, all of whom had previously received some antithyroid treatment.

The analysis brings to light examples of the misuse of these drugs. The most common faults include failure to control the hyperthyroidism completely, usually as the result of inadequate dosage; improper selection of cases for prolonged medical treatment, such as intrathoracic goiters, very large adenomatous goiters or large exophthalmic goiters; mistaken diagnosis—chiefly the use of prolonged antithyroid treatment in patients with anxiety neurosis; the use of dosages of drugs which are so small as to accomplish little beyond exposing the patient to the possibility of drug sensitivity.

The preoperative use of thiouracil drugs is well established.

A summary of the present status of prolonged use of thiouracil drugs as a form of medical treatment is presented.

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Seminars on Pulmonary Physiology

Mechanics of Respiration*

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THE mechanics of breathing is a problem requiring on one hand the detailed knowledge of a classical anatomist and on the other hand the analytic understanding of an engineer. The anatomists have clearly presented their side of the subject and their conclusions have duly penetrated to the pages of current textbooks. It is amazing, however, to discover how superficial has been the analysis of the engineering aspects of the subject by physiologists. Perhaps it is because, to most physiologists, chemistry has seemed a more fruitful tool than physics; or more likely because the flow of air through tubes seemed too simple for serious attention or of too little practical value to medicine. Be that as it may, this chapter will strive to present an analysis of the problem from the point of view of an engineer who may wish to know for the breathing machinery of man the stresses and strains, limiting factors, reserves, power loads and work loads. No two men are the same and it will be necessary to use average values where they are available and individual values where averages are lacking. However, the methods are applicable to abnormal as well as to normal individuals and an accurate scientific description of an individual breathing apparatus can hardly fail to have practical value.

One of the first pieces of information which an engineer would wish to have concerning any pump is the stress-strain or the pressure-volume diagram. This is given in Figure 1 for the human chest and lungs (Rahn et al. 1946). Volumes in per cent of the vital capacity are plotted vertically while pressures, positive and negative, are plotted horizontally.

Maximum Inspiratory and Expiratory Pressures. The outer boundaries of the diagram are formed by the maximum inspiratory and expiratory pressures which can be exerted at different lung volumes. The pressures are measured simply by expiring and inspiring with maximum effort against a mercury manometer with care to avoid the use of the cheeks in blowing or the tongue in sucking. The corresponding volume is measured from a recording spirometer in the breathing circuit using as a reference point the relaxation volume, Vr, which is reached at the end of a normal passive expiration. After reaching the desired volume the subject is switched from the spirometer to the manometer and the resulting maximum inspiratory or expiratory pressure is recorded. The pressure produced is read from the manometer and is plotted against the final volume of the lungs at the time when the pressure is developed. For positive pressures this volume is slightly less than the volume calculated from the spirometer because the pressure compresses all the air in the lung including the residual air. Thus starting from the point of maximum inspiration at zero pressure (Y = 100, X = 0) in Figure 1, pressure is exerted along the slightly curved line represented by the arrow to the right. Similarly, starting from the point of maximum expiration at ambient pressure (Y = 0, X = 0), inspiratory pressure is exerted to the left along the slightly rising arrow. This arrow slopes less than the one for positive pressures because the total lung volume is confined to the residual

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air and does not include also the vital capacity.

These curves for maximum inspiratory and expiratory pressures outline the total range of pressures and volumes which can be concerned in any respiratory maneuver.

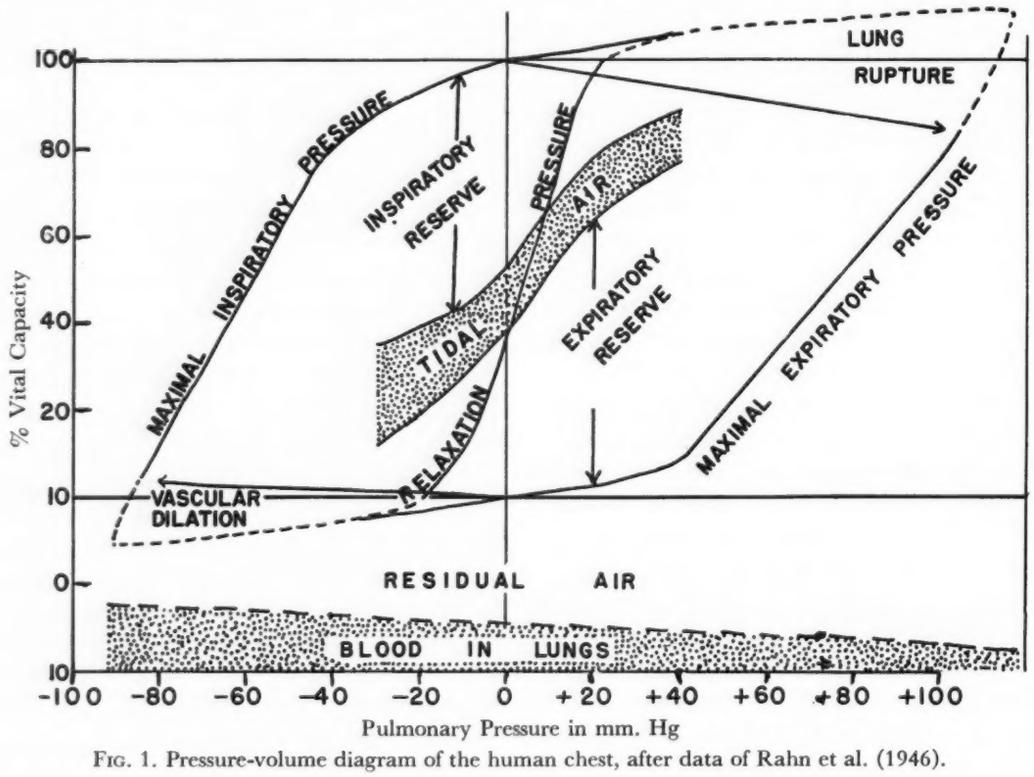

FIG. 1. Pressure-volume diagram of the human chest, after data of Rahn et al. (1946).

No pressures greater than this can be attained either positive or negative unless this is done by artificial means. The right side of the diagram at relatively low pressures is the area concerned in continuous pressure breathing for therapy or intermittent pressure breathing for artificial respiration. At higher pressures of 40 to 50 mm. Hg air may begin to leak through the connective tissue of the bronchioles and penetrate through the mediastinum to produce interstitial emphysema in the neck or abdomen (Katz, 1909; Kronecker, 1909). At still higher pressures of 60 to 100 mm. Hg (Henry, 1945) the lungs are likely to rupture. The dotted line, representing expiratory pressures on the right side of the chart are unexplored because of this danger of damage to the lungs. Accidents have occurred in this region in sailors practicing submarine escape technics (Polack and Adams, 1932). If the breath is held during the ascent, the pressure rises to dangerous levels and may force air into the blood vessels and cause cerebral emboli. Likewise in explosive decompression, which would result from sudden loss of cabin pressure in a stratosphere plane, the chest is maximally expanded until the excess air can escape.

In the process of defecation the pulmonary pressure may be very high but there is little strain on the lung because it is not markedly expanded. The negative side of the chart is concerned in all inspirations. Rather high relative negative pressures may be attained in subjects immersed in water and breathing ambient pressure through a tube reaching to the surface. In such an experiment the inspiratory pressure curve indicates the maximum depth at which inspiration is possible at all lung volumes. According to the chart the maximum inspiratory pressure is about 80 mm. A recent study of this question (Mackay, 1948) has placed 5 feet of water as the limiting depth beyond which inspiration becomes impossi-

ble. This would correspond to about 112 mm. Hg. In such an experiment the pressure in the lungs is not negative relative to the atmospheric pressure but is negative relative to the pressure in the water surrounding the body, so that the differential effect is identical to that produced by the application of an equal negative pressure to the lungs. Extreme negative pressures, indicated by the dotted lines, have not been explored because of the danger of overdilating the blood vessels and the possibility of pulmonary hemorrhage. One experiment of this sort (Stigler, 1911) was reported to have resulted in a dilated heart.

Vital Capacity. Vertical distance at any point on the abscissas in Figure 1 between the inspiratory and expiratory pressure lines represents vital capacity. In theory, therefore, the diagram could have been obtained by measurements of vital capacity at different pressures although safety considerations would have limited the data to pressures of 40 mm. and less. It will be observed that small changes in pressure in either direction have little effect upon the vital capacity but at larger pressures, both positive and negative, the vital capacity diminishes and ultimately reaches zero at some undetermined point. Both the inspiratory and the expiratory pressure curves have been continued as solid lines for some distance beyond the line of zero pressure. Over this area vital capacities have been measured in thirteen normal individuals (Rahn, Otis, Chadwick and Fenn, 1946) and the lines drawn are in accord with the resultant findings. It is furthermore reasonable to expect that the volume of maximum inspiration can be somewhat increased when the subject is aided by some positive pressure in the lungs and vice versa. This effect is indicated in the chart.

Expiratory and Inspiratory Reserves. These fractions of the vital capacity are indicated in Figure 1. The expiratory reserve is the fraction between the end of a normal expiration and the point of maximum expiration. The inspiratory reserve is the volume between the end of a normal inspiration and the maximum inspiration at the same pressure. These terms are preferred to the former terms complemental and supplemental air because they are self-explanatory. They have been recommended for use by a committee on respiratory terminology which reported recently.*

Residual Air. It will be noticed in Figure 1 that the residual air varies markedly with pressure, being much greater at positive pressures and somewhat smaller at negative pressures. On the positive pressure side, this increase in residual air results chiefly from the inability of the expiratory muscles to deflate the chest to the usual degree against the positive pressure in the lungs. A further factor of minor importance is the variation in the amount of blood in the chest. This is diminished at positive pressure but increased at negative pressure. Such changes in the amount of blood cause corresponding changes in the space available for residual air. For this reason the lower boundary of the residual air in Figure 1 is not horizontal. The shaded area represents varying amounts of blood in the lungs. This part of the diagram is somewhat schematic because accurate data are not yet available. Present data indicate that 200 to 500 cc. of blood can be forced out of the lung by positive pressure (Fenn et al. 1947).

Relaxation Pressure Curve. The pressure-volume curve for passive inspiration and passive expiration is called the "relaxation pressure curve" (Rahn et al. 1946). This has an "S" shape as shown in Figure 1 and crosses the vertical axis at Vr, which is the relaxation volume at ambient pressure and corresponds to the end of a normal expiration. The stippled area marks the position of the tidal air while breathing voluntarily at different positive and negative pressures. The relations between these two can be described after a further account of the relaxation pressure curve has been given.

Relaxation pressure curves can be obtained by two different methods: (1) by measuring volume changes resulting from different pressures and (2) by measuring pressure changes occurring at different volumes.

* *Federation Proc.*, 9: 602, 1950.

The first of these methods was utilized by Jaquet in 1908 and Bernoulli in 1911 who were the first to obtain curves of this type. The subjects were in a closed chamber breathing through a tube held in the mouth and connected to a spirometer outside of the chamber. Rhythmical variations in pressure were applied to the interior of the chamber causing rhythmical inflations and deflations of the chest which were recorded on the spirometer. Therefore, this represents an early application of the principle of the Drinker respirator. By varying the pressures in steps of 15 mm. Hg from −40 to +40 mm. Bernoulli was able to plot the whole resting pressure-volume diagram.

As a second method, similar data may be secured by voluntarily inflating the chest to a known value, starting from the point of complete relaxation then connecting the lungs to a manometer by a tube inserted in one of the external nares (Rahn et al. 1946). When the inflated chest relaxes a positive pressure is developed. If the chest is first deflated by a forceful expiration, a negative pressure is developed in the manometer when the muscles are relaxed. From this procedure the curve derives its name of relaxation-pressure curve. No careful comparison has ever been made between the curves obtained by these two different methods but presumably they would be identical if the respiratory muscles are completely and equally relaxed in both cases. The curve is useful in showing the pressures which would have to be applied by an artificial respiration apparatus in order to produce any desired change in volume or any desired tidal air.

The most complete data on relaxation pressures are those of Rahn et al., 1946, from data on fourteen subjects. Over the normal physiologic range the slope was found to be 94 cc. per mm. Hg. For experimental purposes the elastic characteristics of the chest can, therefore, be simulated by the use of a rigid chamber of 71 L. capacity since the addition of 94 cc. of air will raise the pressure by 1 mm. as in the human lung. There are considerable differences in this slope in different individuals but there has been no study which permits any correlation between this slope and any other characteristics of the individual such as age or body weight.

The effect of posture on the relaxation pressure curve was first studied in a single subject by Rohrer (1916, 1925) who found that it was shifted to the right (Fig. 3) when the posture was changed from the erect to the supine position. A still further shift in the same direction was produced by the head-down position. These data were largely confirmed by Rahn et al., 1946, although there seemed to be no change at the larger lung volumes in their data. As an average value in thirteen men it was found that the relaxation pressure at the end of a normal expiration increased 7.5 mm. Hg when the position was changed from the erect to the supine position. This is about equal to the average pressure over the diaphragm due to the fluid abdominal contents in the supine position if the diameter of the thorax is considered to be 20 cm. The change in the relaxation pressure curve, therefore, is presumably due to the weight of the viscera.

Tidal Air. The tidal air band in Figure 1 shows the lung volumes which are instinctively selected when breathing against different positive and negative pressures (Rahn et al. 1946). It is evident that at ambient pressure the lower edge of the tidal air band coincides with the relaxation pressure curve. This means that expiration is passive. At a positive pressure of 9 mm. Hg it is the upper or inspiratory edge of the tidal air which becomes the point of relaxation. At this point inspiration becomes entirely passive while expiration is active. With still higher pressures the chest never comes to rest throughout the breathing cycle but the subject continuously exerts some expiratory pressure even at the height of inspiration. When breathing against negative pressures, likewise, there is no point of relaxation but in this case a continuous inspiratory pressure is exerted to prevent the chest from collapsing.

Lung Elasticity and Chest Elasticity. The

relaxation pressure curve can be further analyzed into its two components, that due to the elasticity of the lung and that due to all the other elastic structures in the chest including the diaphragm, the chest walls and the abdominal wall. This is illustrated by the curves in Figure 2 where a relaxation pressure curve is plotted as a solid line and the probable pressure-volume diagrams of the lung and the chest (including the diaphragm, etc.) as dotted lines. At the relaxation volume, Vr, the pressures exerted by the chest and the lungs are equal and opposite. The chest tends to expand with a pressure equal to the collapsing pressure of the lungs. At a volume of about 53 per cent of the vital capacity the chest attains its resting position, this being the point where the P-V curve of the chest crosses the Y axis.* At the same volume the lung elasticity curve crosses the relaxation pressure curve. At this point all of the relaxation pressure is due to the lung elasticity. In a pneumothorax when the lung collapses the chest should expand to its resting point.

Since the lung is always tending to pull away from the chest, there is potentially a negative pressure between the lung and the chest in the intrapleural "space." Because of this negative pressure it might be anticipated that gas bubbles would tend to accumulate until an actual space appears. That this does not happen is due to the peculiar shape of the oxygen dissociation curve. According to this curve the fall in oxygen pressure caused by the removal of a given volume of oxygen from the arterial blood is far greater than the rise of carbon dioxide tension caused by the addition of an approximately equal amount of carbon dioxide. For this reason the sum of the tensions of the dissolved gases in the venous blood and the tissues generally is always less than that in the arterial blood and less than the total pressure in any bubble inserted into the intrapleural space. The bubble is, therefore, absorbed because the partial pressures of the gases are always less in the tissues than they are in the bubble. It is not always realized that the whole mechanism of breathing by the lungs would be impossible if it were not for this remarkable mechanism. It is the same mechanism, of course, which causes the absorption of gas in an artificial pneumothorax. One cannot help wondering naively whether this particular advantage of the shape of the oxygen dissociation curve of blood was "realized" when the human breathing mechanism was first "invented." Without it, however, the whole "machine" would have been a failure.

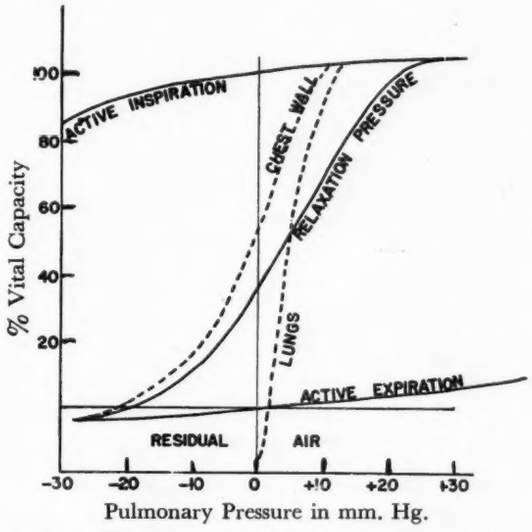

FIG. 2. Relaxation-pressure curve (solid line)—average data from fourteen subjects of Rahn et al. (1946). Dotted lines represent best guess as to the pressure-volume curves of the passive chest and lung separately. Portions of the active pressure-volume curves are also shown.

The pressure volume curve of the isolated lung was first measured by Liebermeister (1907) on one lobe of a human lung removed immediately after death from an executed criminal. He found that lungs from autopsies gave erratic results. A very similar curve for a dog lung is shown in Figure 3 from the work of Romanoff (1910). The "S" shape of this curve has more recently been confirmed by Lawton and King (1949) who pointed out the resem-

* This crossing was previously taken to be at 72 per cent of the vital capacity because the emphysematous chest expands to that degree, presumably due to loss of lung elasticity (Rahn et al. 1946). There may, however, be other changes in emphysema in addition to those in the lung itself and the new value of 53 per cent fits better with new concepts concerning the S-shape of the lung elasticity curve.

blance to the P-V curve obtained from a rubber bag. According to the theory of extensibility of rubber there should be a middle portion of high extensibility where the arrangement of the chain molecules becomes less random and the entropy decreases as the volume increases. At smaller volumes greater resistance to expansion is offered by molecular forces and at larger volumes the rubber stiffens because of a sort of crystallization process (King and Lawton, 1950). Although this simple explanation seems quite adequate, some anatomic factors might also be involved. Be that as it may, over the physiologic range the expansion of the lung seems to be a linear function of the volume (Cloetta, 1913). The expansion of the lung per mm. Hg over this range is 27 per cent of the vital capacity according to Liebermeister (1907) and probably 16 per cent for laboratory animals according to Romanoff (1910). The uncertainty in the latter case is due to lack of precise information as to the fraction of the curve (Fig. 3) which can be assigned to the vital capacity (900 cc. has been assumed). The steepest part of the lung elasticity curve of Figure 2 has a slope of about 15 per cent per mm. Hg.

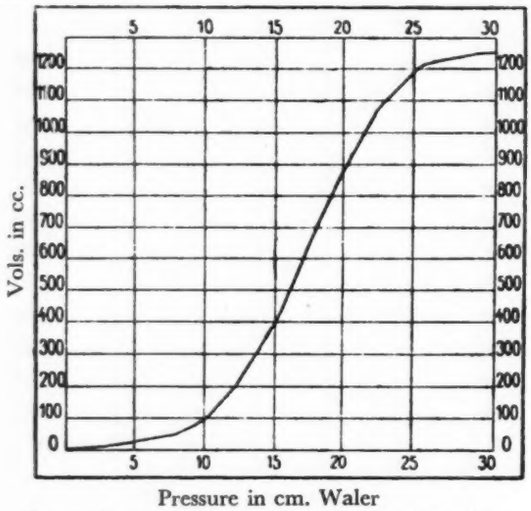

FIG. 3. Pressure-volume curve of a dog lung, from Romanoff (1910).

The lung elasticity can be measured *in vivo* by recording the intrapleural pressure during quiet breathing at different tidal volumes. Such records were first adequately studied by Neergaard and Wirz (1927) who pointed out that the elasticity of the lung could be measured at the points where the velocity of air movement was zero, i.e., at the points where the direction of flow was reversing. While air is moving or the lungs are expanding, there are pressure differences caused by the pressure gradient required to move the air either in or out and the pressure required to deform the lungs. A record of intrathoracic pressure coupled with a record of the velocity of flow of the air permits a measure of both lung elasticity and the resistance to movement. A typical record is shown in Figure 4 in which P.T. represents the pneumotachogram and Pl.Dr. the intrapleural pressure record. The value Pl.Dr. at points where P.T. crosses the zero line (oL.), as for example Ph, is a measure of the lung elasticity. The line Pl. stat., therefore, represents the static elastic pressure. Deviations from this value are due chiefly to the pressure required to move the air.

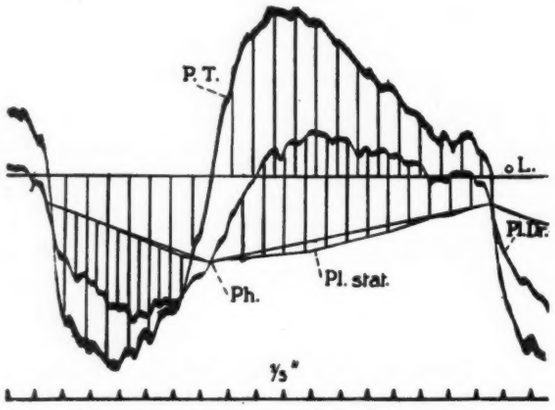

FIG. 4. Intrapleural pressures (Pl. Dr.) in an emphysematous patient and simultaneous record of the velocity of flow (PT = pneumotachogram), from Neergaard and Wirz (1927).

Values for the lung elasticity can also be approximated indirectly by simultaneous measurements of the venous pressure, pulmonary pressure and pulmonary volume. This method is based upon the assumption that changes in the intrapleural pressure are reflected by equal changes in the venous pressure. This is more nearly true of the right auricular pressure but even the pe-

ripheral venous pressure follows the intrapleural pressure, qualitatively at least, but with a slight lag depending upon the rate of blood flow. So long as the lung volume remains constant, an increase in pulmonary pressure results in an equal increase in venous pressure. If, however, the lung is allowed to expand when pressure is applied to the trachea, only a fraction of the applied pressure appears as an increase in the venous or the intrapleural pressure because some of the applied pressure is absorbed in the elastic walls of the lungs. Under normal conditions about half of the applied pressure is passed on to the intrapleural space or to the venous blood. Proceeding in this way Otis, Rahn and Fenn (1946) obtained a value for the extensibility of the lung of about 5.7 per cent of the vital capacity per mm. Hg. This agreed with a similar estimate by Rohrer (1915) and was even higher than estimates by Neergaard and Wirz (1927) and Christie and McIntosh (1934). This value fits well with the suggestion that the expansion of the chest to 72 per cent of the vital capacity in emphysema is due to complete loss of lung elasticity but it does not accord with an "S"-shape curve for lung elasticity (Lawton and King, 1949) and is probably too low. Therefore, it is possible that other factors contribute to the expansion of the emphysematous chest. Figure 2 is drawn with the steeper lung elasticity slope and the "S"-shaped curve but its correct position is not well established.

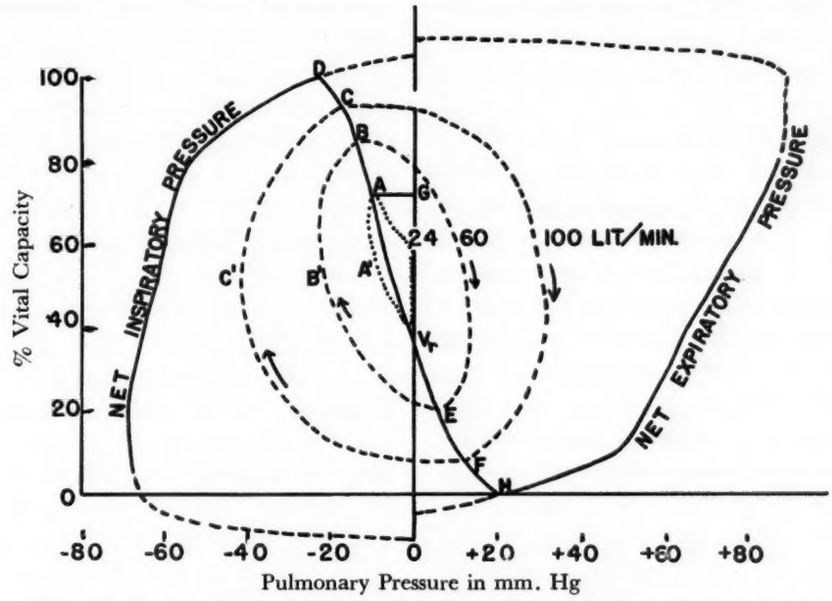

FIG. 5. Net maximum voluntary inspiratory and expiratory pressures. The pressures required to balance the relaxation pressures are indicated by line HD. Three respiratory loops for three different ventilation rates (as indicated) are represented by dotted lines A′, B′ and C′. Areas of these loops represent the work required for these ventilation rates.

Net Voluntary Pressures. The maximum pressure recorded at each volume in Figure 1 represents the algebraic sum of passive and active pressures. The net pressure produced by the contraction of the respiratory muscles is obtained by subtracting the relaxation pressures from the maximum voluntary inspiratory and expiratory pressures at every volume. The outer curves plotted in Figure 5 represent these differences. A mirror image of the relaxation pressure curve of Figure 1 is also plotted in Figure 5. In this case it represents the inspiratory or expiratory force which must be exerted in order to balance the relaxation pressure and so produce corresponding increases or decreases in the volume of the chest.

The area between the relaxation pressure curve and the Y axis represents the elastic work required to inflate or deflate the chest,

starting from the relaxation volume Vr. This is the work which would actually be required if the change in volume occurred so slowly that frictional resistance was negligible. In ordinary breathing this is not the case and the dotted line VrA′A represents the pressures actually required in increasing the volume 1.6 L. from Vr to G at a frequency of 15 per minute. The total work done during this inspiration is VrA′AG. During expiration the potential energy VrAG is available to accomplish the work of expiration. In this case the potential energy stored in inspiration is more than sufficient for expiration since the expiratory loop (indicated by the dotted line to the right of VrA) is entirely covered by the triangle VrAG. This is no longer the case at higher ventilation rates as indicated by the two other respiratory loops for 60 and 100 L. per minute as shown in Figure 5. To the extent that these loops overlap to the expiratory side of the diagram it will be necessary to make use of active expiratory effort to accomplish the ventilation required. It is interesting to note what a small fraction of the total area of the pressure volume diagram is required for normal breathing, only about 0.3 per cent. Even in breathing at the high rate of 100 L. per minute (FC′C) only about one-third of the total is needed. If the subject could increase his tidal volume, however, to 100 per cent or 4.7 L. and his frequency to 30 per minute the calculated work becomes 7.1 kg.m. while the total area of the PV diagram is 8.7 kg.m. This, of course, does not prove that an individual represented by the diagram of Figure 5 should be able to breathe at the high rate of 4.7 × 30 or 141 L. per minute. The rate with which he can bring his reserve forces into play is a limiting factor as well as the actual magnitude of these forces.

This discussion has provided an over-all picture of the work of breathing and its relation to the total energy available. It is necessary now to indicate how these respiratory loops were calculated or measured and to describe how the different fractions of the respiratory work are evaluated.

Measurement of Work of Respiration in Drinker Respirator. The respiratory loop VrA′A in Figure 5 was measured by placing a subject in a Drinker respirator and providing passive ventilation. The subject was instructed to relax as completely as possible and to permit the machine to ventilate his lungs without any effort on his part. The pressure inside the respirator was continuously recorded. The velocity of the air which passed in and out through the mouthpiece was recorded at the same time by means of a pneumotachogram or flowmeter. The volume of the chest was determined by integration of the flow curve at successive points. As an alternative, and for this purpose a simpler method, a subject could have breathed in and out of a recording spirometer. If the pressures in the respirator are plotted against the simultaneous volumes on the spirometer, measured from the relaxation volume, Vr, as a base line, the loop VrA′A is the result. To produce this same rate of breathing voluntarily the muscles will have to exert a pressure equal to that provided by the respirator. In this case the total work of the respiratory cycle is not the area of the loop alone but rather the slightly larger area VrA′AG. That part of the potential energy VrAG which was not needed for moving the air, i.e., the area outside the loop, represents energy used in working against the air pressure in the machine during expiration.

The other respiratory loops in Figure 5 are only diagrammatic but their total areas were determined by calculation in a manner to be described later.

Theoretic Resistance to Air Flow. The resistance of the airway was studied by Rohrer in 1905 (cf. also 1925) in an exhaustive manner. It is extraordinary that so little attention has been paid to this admirable contribution. He measured carefully the lengths and the diameters of the various sections of the air way and calculated the resistance of the whole system. The equation which he arrived at on theoretic grounds came very close to the value determined later experimentally.

For the most part the flow of air is laminar or streamlined rather than turbulent. For laminar flow the pressure drop, p, required for a given velocity of flow, v, is given according to Poiseuille's law by the equation (Equation 1):

$$p = \frac{8l.v.\eta}{981.r^2} = \frac{kV}{r^4}$$

where p is in cm. of H_2O, v is in cm. per sec., r is the radius in m., l is the length in cm. and η is the viscosity which in absolute units equals 0.0001873. V is the volume flow in liters per second and k is a constant.

When the velocity, v, exceeds a critical value, the flow becomes turbulent and the pressure drop varies as v^n where n has a value between 1.7 and 2.0. The critical velocity (in cm. per sec.) for turbulent flow equals

$$\frac{1290\eta}{d\gamma} = \frac{216}{d}$$

where η is the viscosity, γ the density of air (relative to water) and d is the diameter in mm. For the human trachea with a diameter of 21 mm. the critical velocity is 10.3 m./sec. or 216 L./sec. which is far in excess of any velocity attainable except perhaps momentarily in a cough. The velocity of air flow in the different parts of the airway (relative to the tracheal velocity as 1.0) is 3.39 in the glottis, 1.70 at the nasal openings; it reaches a second maximum of 1.64 in the bronchioles of 6 mm. diameter and diminishes to zero with some minor fluctuations in the smallest alveolar ducts. There is little likelihood, therefore, of exceeding the critical velocity anywhere in the airway. Turbulence does develop, however, for other reasons when the air changes direction rapidly as in the nasopharynx or when the diameter of the air way is abruptly altered as it is at the glottis. The pressure drop at all such points increases as the square of the velocity. The complete equation (Equation 2), therefore, for the pressure drop is:

$$p = 0.79V + 0.801V^2$$

where p is in cm. H_2O and V is L./second. Here the first term is for streamline resistance (as in Equation 1) and the second for turbulent resistance at particular points in the airway. The division of the resistance between the upper airway (trachea and above) and the lower airway or bronchopulmonary systems can be deduced from the following equations from Rohrer:

Upper airway $\quad p = 0.426V + 0.7135V^2$
Lower airway $\quad p = 0.364V + 0.0875V^2$

The turbulent fraction is, therefore, far greater in the upper airway and increases rapidly with the velocity.

Rohrer estimates that when the rate of ventilation increases from 6 to 60 L./minute, the percentage of the total resistance which is due to turbulence increases from 10 to 50 per cent. In both cases, however, nine-tenths of the turbulence occurs above the trachea. The fraction of the total resistance which occurs above the trachea is 58 per cent at 6 L./minute and 71 per cent at 60 L./minute. While more than half of the total resistance to breathing is located above the trachea in the larger passages, it is interesting that below the trachea the resistance increases as the vessels become smaller. In the ultimate lobules Rohrer estimates that the tubes branch dichotomously in such a way that each branch is 0.82 as long and 0.82 as wide as the parent tube. At each branching, therefore, the resistance per unit of length increases

$$\frac{1}{2.r^4} = \frac{1}{2 \times 0.82^4} = 1.1 \text{ times.}$$

When the smallest passages become partially obstructed by the accumulation of fluid, turbulence does develop and is recognized by the diagnostician as rales in the stethoscope. Turbulence is also produced at the glottis when the vocal cords are still further approximated and results in phonation.

Measurement of Resistance to Air Flow. A method of verifying Rohrer's equation was provided by the suggestion of Vuilleumier that the pressure gradient between the mouth and the alveoli could be measured

by the intermittent interruption of the flow. This method was taken up in the writer's laboratory by Otis and Proctor (1948) who confirmed the equation but obtained somewhat different values for the constants. The method consists in momentarily interrupting the flow of air during quiet breathing by closing a slide across the breathing tube. The slide is actuated by a solenoid and is returned to its original position in a fraction of a second by a strong spring. The brief interruption of the breathing is not perceptible to the subject. Simultaneous measurements are made of the pressure between the shutter and the lungs and the rate of flow as indicated by a flowmeter on the "far" side of the shutter. When the flow of air is interrupted during inspiration, the flow record goes to zero and the pressure at the mouth falls to a value which is nearly equal to the low pressure existing in the relatively large volume of the alveolar air at that instant. The change in pressure at the mouth indicates, therefore, the pressure gradient required to cause air to flow at the velocity recorded immediately prior to the interruption. When these pressures are plotted against the corresponding velocities, curves like those in Figure 6 are obtained. The slope of this curve may be taken as a measure of the resistance of the airway. The method lacks something of precision and the points scatter rather widely but the average can be described by the equation (Equation 3):

$$P = 3.5V + 1.5V^2$$

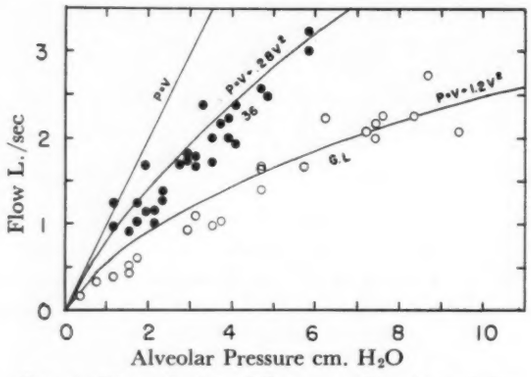

FIG. 6. The velocity of flow as a function of the pressure gradient in a subject breathing at ground level (G. L.) and at 36,000 feet simulated altitude. (From Otis and Bembower 1949.)

where P is in cm. of H_2O and V is in L./second.

The values of these constants have been studied at high altitudes and in helium breathing by Otis and Bembower (1949). One of their graphs for an individual breathing at ground level (G.L.) and at 36,000 feet simulated altitude is shown in Figure 6. The purely viscous resistance to laminar flow is shown by the curve P = V. The addition of the turbulent factor KV^2 is shown by the deviations of the experimental curves from this straight line. Since normal breathing is at the peak rate of about 0.3 L./second, it is evident that for the most part these curves describe relatively high rates of ventilation. The substitution of helium for nitrogen in breathing at ground level changes the density of the gas and provides a curve very similar to that given in Figure 6 for high altitudes. The change in density is about the same in each case and only the turbulence factor is affected. This explanation for the effect of helium on the breathing was also provided by Dean and Visscher (1941).

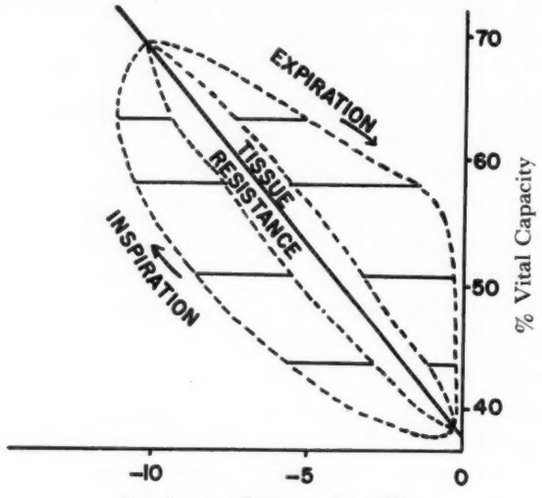

FIG. 7. A respiratory loop on the pressure-volume diagram obtained by passive ventilation in a Drinker respirator. Simultaneous values of pressure and volume provide the dotted lines. The solid diagonal is the relaxation pressure curve. (Redrawn from Otis, Fenn and Rahn 1950.)

With this equation for air flow available it is possible to pursue further the analysis of the work of breathing as measured on the Drinker respirator in a passive subject. In

this method continuous records are taken of the velocity of flow, V. Using these measured values of V for Equation 3 it is possible to calculate the corresponding pressure gradients which would be required. The result can be indicated in Figure 7 which shows an enlarged drawing of the respiratory loop VrA′A of Figure 5. These calculated flow gradients are laid off for both inspiration and expiration as horizontal lines at various points in the respiratory cycle. The area so marked out represents the work required to move the air and the remaining area in the middle of the loop represents work required to deform the tissues of the lung and chest, i.e., viscous work degraded to heat in those tissues. This work is presumably largely proportional to the velocity of movement but it has been empirically analyzed by Otis, Fenn and Rahn (1950) into two factors corresponding to the two terms of the air flow equation but with different constants. From data on three subjects by the respirator technic, Otis, Fenn and Rahn (1950) estimated for the work of inspiration at 15 per minute that 63 per cent was due to elastic forces, 28.5 per cent to air movement and 8.2 per cent to tissue resistance. Similar estimates based on artificial respiration of dogs by Bayliss and Robertson (1939) and Dean and Visscher (1941) attribute rather less to air resistance and more to the other two factors.

Calculation of Work of Breathing. The total pressure required for breathing is given by the equation (Equation 4):

$$P = KV + K'\left(\frac{dV}{dt}\right) + K''\left(\frac{dV}{dt}\right)^2$$

Here P is in cm. H_2O, t is in seconds and V is in L. The first term is the elastic pressure, the second the resistance due to viscosity and the third that due to turbulence. The constants K, K′ and K″ have average values of 8.5, 3.5 and 1.5, respectively. If the velocity of air flow were constant throughout each phase of respiration, it would be easy to calculate the work of breathing by multiplying this force by the volume of air moved per second. Since, however, the velocity of flow varies, it is necessary to integrate the force over the whole volume change which occurs during the cycle. To do this some mathematical shape to the flow pattern must be assumed. One of the simplest assumptions is that the breathing follows a sine curve or $dV/dt = a \sin bt$ and $b/2\pi = f$, the frequency of breathing per second. Using these assumptions the following equation was arrived at for W, the mean total rate of work of inspiration (in kgm. cm. per sec.) with a tidal volume of V liters and a frequency of f breaths per second (Equation 5):

$$W = \frac{1}{2}fKV_T^2 + \frac{1}{4}K''\pi^2f^2V_T^2 + \frac{2}{3}K''\pi^2f^3V_T^3$$

Using this equation calculations have been made of the work required for the various ventilation volumes and frequencies used by Liljestrand (1918) in his measurements of the extra oxygen consumed for respiration. Both work and extra oxygen were converted into the same units and the ratio of the two values determined. This indicates that breathing is carried on with an efficiency of about 5 per cent.

Optimal Frequency for Breathing. For a given alveolar ventilation there must be a certain frequency of breathing which will require minimum work. If the frequency is too high, the tidal volumes are small and the dead space ventilation is a large fraction of the total. If, on the other hand, the frequency is too low, the tidals are too large. A large tidal volume is disadvantageous because the elastic work increases as the square of the tidal volume. This is evident because the elastic work of breathing is represented by the triangular area between the relaxation pressure curve and the Y axis. The area is equal to PV/2. But P = KV. Hence the work is $KV^2/2$. This is the first term of the work equation for inspiration (Equation 5). The optimum frequency for a given alveolar ventilation can readily be calculated if the tidal volume in Equation 5 be replaced by the Equation V = A + d where A and d are the alveolar and the dead space fractions of the tidal volume. The

work equation is then multiplied through by f (no. of breaths per sec.) to obtain the work per second and the quantity Af is put equal to Va (the alveolar ventilation) and treated as a constant. This equation is then differentiated with respect to f and put

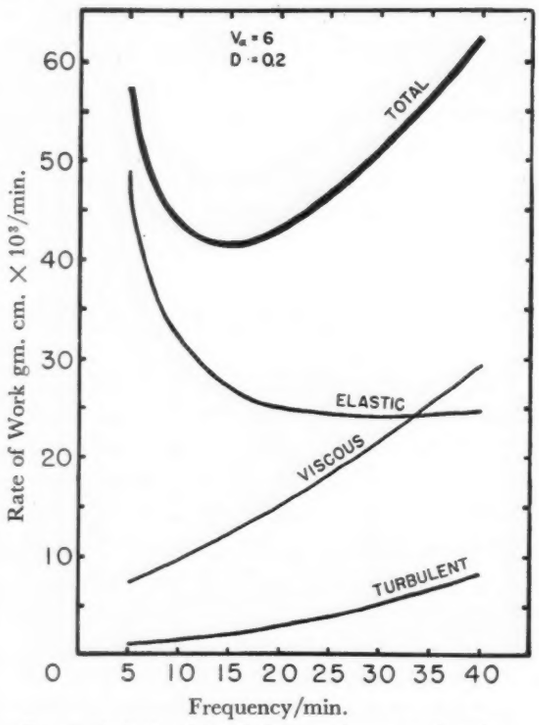

FIG. 8. Relationship of elastic, viscous and turbulent fractions of the total work of breathing at a rate of 6 L. per minute using different frequencies. Values calculated according to a modification of equation 5 after Otis, Fenn and Rahn 1950.

equal to zero to obtain the optimum. In this way it is found that for an alveolar ventilation of 6 L./minute the optimum frequency is 15 breaths per minute. For resting conditions, therefore, it appears that man instinctively chooses a frequency of breathing which is close to the point required for minimum work. From an economic point of view this may not seem very important because the total cost of breathing per day is covered by the energy derived from one candy bar or less; but the observation is perhaps important from a philosophic point of view. The principle of minimum work seems to govern most of the responses of living organisms.

It is instructive to plot out the values of the different fractions of the work of breathing as a function of frequency. This has been done according to the method outlined above and the result is shown in Figure 8. The curves represent the work required in the various categories to produce alveolar ventilation of 6 L./minute at the frequencies indicated. The total work is seen to pass through a minimum at a frequency of 15 as already mentioned. The elastic work steadily diminishes as the tidal volumes decrease or the frequency increases. The viscous and turbulent work fractions, however, tend to rise, the former as a linear function of the velocity and the latter as the square of the velocity in accordance with equation 3. At this alveolar ventilation volume of only 6 L./minute the turbulent factor is a small part of the total but at higher minute volumes it increases rapidly.

Equation 5 concerns only the work of inspiration and assumes that expiration is entirely passive. For relatively low rates of ventilation this is true. For higher minute volumes in which all of the elastic potential energy stored in inspiration is used for expiration, the total work for inspiration and expiration is equal to twice the value of the second and third terms of equation 5, without including the first term for elastic work at all. This is evidently true if the velocity pattern in expiration is the same as that in inspiration because, if the elastic work is added to the work of inspiration, it would have to be subtracted from the work of expiration. Derived in this way the total work per second is given by the following equation (Equation 6):

$$W = \frac{1}{2} K'\pi^2 f^2 V_T^2 + \frac{4}{3} K''\pi^2 f^3 V_T^3$$

where W = kg.cm. per sec., f is breaths per sec., V_T is tidal volume in L. and K′ and K″ are constants with values of 3.5 and 1.5, respectively (for the three cases given by Otis et al. 1950). This equation was used for the calculation of the work areas of the respiratory loops in Figure 5 for ventilation rates of 60 and 100 L./minute. For such high ventilation rates equation 5 (for in-

spiration alone) would give too low values and conversely for low ventilation rates equation 6 would give too low values. It is apparently not possible to provide an equation which will cover adequately all rates of ventilation and for intermediate values it is necessary to try both equations and use the larger value.

Action of Respiratory Muscles. It may be pertinent to add one final word concerning the action of the respiratory muscles themselves. The total area of a pressure volume diagram represents the total work which could conceivably be performed by all of these muscles in transporting air in or out of the lungs. The muscles themselves, however, merely work by shortening under tension. When the external intercostals shorten, they cause the ribs to rise and the internal intercostals do the reverse. The area of the pressure volume diagram must eventually derive from the summation of the areas of all the length-tension diagrams of the individual muscles concerned in respiration. It has been possible from anatomic data in the older German literature to estimate the total cross sectional area of the intercostal muscles and the absolute amount of shortening which can occur between points of maximum inspiration and maximum expiration. Assuming that these muscles produce the same force per square cm. of cross section area as do other skeletal muscles when maximally innervated, it is possible to calculate the total work which they could conceivably perform. This would be the product of the total force by the maximum amount of shortening. It is interesting to find that this method predicts an area of the pressure volume curve which is between 8 and 13.5 kg.m. The actual area of the pressure volume diagram in Figure 5 was 8.7 kg.m. The contribution of accessory muscles of respiration, particularly the diaphragm, is omitted from these estimates but the agreement is surprisingly good.

These considerations reveal also the fact that the respiratory muscles are able to shorten by an appreciable fraction of their own length. This is necessary for the efficient performance of work. If they shorten too much, the tension is too low and if they shorten too little the work performed is too small. Their working conditions for respiration are evidently no less advantageous than those of other skeletal muscles.

SUMMARY

This outline of the mechanics of breathing is not altogether new and is largely a summary of recent work on the subject from the author's laboratory. The data apply primarily to normal healthy young males and the variations to be expected in other age groups and in clinical practice are still unknown. The outline is unsatisfactory also because of inadequate information concerning the elasticity of the human lung and its proper position on the pressure-volume diagram. No attempt has been made to deal separately with abdominal and thoracic types of breathing and indeed the data for this purpose are non-existent. The distribution of resistance to air flow between the upper and lower respiratory passages is not well documented experimentally and would be of much clinical interest. At best, an outline of the mechanical problems of breathing has been sketched and some possible methods of attack have been suggested for future additions to our knowledge of the subject.

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Conference on Therapy

Management of the Menopause

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. RALPH W. GAUSE: The subject for today is the treatment of the menopause. Before introducing the speaker I should like to express a personal opinion which I hold with firm conviction. I strongly believe that the menopause should be treated by the doctor who knows the patient best, not necessarily by one who knows the disease best. The patient's emotional state and personal problems are more important than medicines. They are much harder to manage than the purely medicinal problems. The doctor who knows the patient well and who has inspired the patient with confidence in him is the one to treat her menopause. Beyond that it is a matter of indifference whether he is a general practitioner, surgeon or anything else. A woman's reaction to the menopause is variable and individual. Therapy must be varied and individualized to the same extent. And now, Dr. Shorr.

DR. EPHRAIM SHORR: It seems that about every four years I am asked to talk about the menopause. When the topic was suggested for this conference, I reviewed an article of mine published in 1940, and I compared the text with our knowledge of the subject as it stands at the present time. I was chagrined to discover how little I had learned in that period. I therefore thought that if I were to start with that paper and indicate the changes which have resulted from the enlarged experience I could at least make a progress report on the subject.

What is the menopause? It appears to be the consequence of the spontaneous waning of ovarian activity which takes place at about the age of forty-seven, much earlier in some and later in others, or the consequence of surgical removal of the ovaries. It is associated with certain endocrine alterations, namely, a profound reduction in the amount of circulating estrogen and an increase in the urinary titer of follicle-stimulating hormone of the pituitary gland. What causes the symptoms of the menopause? Is the excess of follicle-stimulating hormone responsible for the physiologic alterations which form the basis for the symptomatology or is it the low level of estrogens? Both concepts have been advanced. The fact that menopausal symptoms at times occur without any increase in the titer of the gonadotrophic hormone in the urine makes it more likely that the symptoms are due to the loss of estrogens. This endocrine state is common to all women in the menopausal period; hence it furnishes no explanation for the difference between women, namely, that have marked menopausal symptoms while in others the readjustment is relatively uneventful.

Inasmuch as ovarian insufficiency is the most likely cause of the symptoms, the problem calls for replacement therapy. Up to 1940 we used androgens and estrogens both synthetic and natural. The only change in the management that has occurred since then has been the use of a wide variety of synthetic estrogens. This has confronted the physician with problems of dosage.

In the vaginal smear we have a useful guide to proper dosage of estrogens. With the smear we can readily ascertain whether treatment has been optimal. We can also determine whether a symptom during the menopause, which has persisted despite what appears to be apparently adequate

dosage, is in reality of menopausal origin. For example, if a headache continues after therapy has been started and the vaginal smear has become fully cornified, we may safely attribute the headache to a cause other than the menopause. The same type of vaginal smear we were using successfully in 1940 still remains our best therapeutic index. It will also continue to be useful for the purpose of evaluating claims for relative activity of various estrogens.

The effect of androgens in ameliorating symptoms of the menopause was recognized in 1938. At that time it was found that doses of 25 mg. of testosterone propionate daily were effective in some patients in reducing menopausal symptoms. About four or five years ago when oral preparations became available, the popularity of androgens increased greatly. It appeared that they might even replace the estrogens. We, too, explored the use of the androgens. One theoretic advantage of the androgens was the fact that they did not cause the proliferative endometrial changes produced by estrogens. However, we found to our dismay that relatively few patients obtained adequate symptomatic relief with the doses which failed to produce virilization. [The synthesis of an androgen which would duplicate the estrogen-like effects of testosterone without the virilizing effects has been attempted. There are results which suggest that this may be feasible. Editor.] Androgens prevent the withdrawal bleeding resulting from estrogens. An attempt has therefore been made to secure the beneficial effects of the estrogens on the symptoms of the menopause simultaneously with the effect of androgens in preventing endometrial proliferation by the use of the two agents simultaneously. To discover the proper ratio of the two hormones has presented a difficult problem. An intramuscular dose of 50 mg. of testosterone propionate together with 1 mg. of estradiol benzoate is the ratio which has been most commonly applied. None of the combinations appears to have proved successful.

In this connection I might refer to the problem of cancer production by the estrogens. We were somewhat surprised when a surgeon who has had considerable experience with cancer suggested that there was no appreciable danger in the use of the small amounts of estrogen which might be necessary to relieve the symptoms of the menopause in a patient with cancer. We are seeing an interesting shift in the views on the relationship of exogenous estrogens to neocarcinogenesis. Perhaps I should elaborate on this point because there is so much fear of the hazard of inducing cancer by the estrogens. Hartman and others at Yale administered massive doses of estrogens to monkeys for a number of years. Some received as much as 1,000,000 rat units a year. There was not a single instance of carcinomatous change in any organ. The close relationship of the monkey to man makes these experiments particularly valid in evaluating the dangers of estrogens in humans. However, there is one observation which leaves this problem still undecided, namely, the evidence which suggests that although the administration of estrogens is not likely to produce cancer in humans these compounds may prove harmful in women in whom carcinoma of the breast has already developed.

While we are on this subject, I might mention the need for bearing in mind the matter of pelvic malignancy which arises coincidentally with the menopause. I should stress the desirability of making thorough pelvic examinations before one starts estrogen therapy in the menopause and for repeating the examination periodically during the course of the treatment. The reason is that menstrual irregularities may be attributed to the menopause when the real cause is cancer.

Bleeding is one of the problems of estrogen therapy in the menopause. It occurs most often after the drug is discontinued following a period of treatment. It can be minimized or prevented by the appropriate plan of therapy which takes into account the length of time the estrogen is given and the size of the dose. The duration of treatment should

be inversely proportional to the dose. Thus if a patient receives full biologic replacement dosage, it may be continued for a period of three or four weeks. A rest period then follows; and when the drug is resumed, smaller doses may be given which may be continued for a longer period before another rest period. The intermittent plan of therapy is the most favorable one for reducing or preventing withdrawal bleeding. The rest periods permit gradual involution of the endometrium. They also have the advantage of allowing periodic evaluation of the spontaneous adjustments the patient is making to the menopause.

We are in agreement with the view expressed by Dr. Gause to the effect that emotional and psychologic factors play a major part in the reaction of women to the menopause. Maladjustments before the menopause have a tendency to increase difficulties during the menopause. We have been impressed by the high frequency of the menopausal syndrome in patients with unfavorable emotional adjustments combined with unpleasant personal situations, and we have been equally impressed with the frequency of complete relief of symptoms when personal stresses and maladjustments are corrected. The return of menopausal symptoms two or three years after an apparent adjustment has been made can often be assigned directly to exciting factors in the patient's life situations.

DR. GAUSE: Thank you, Dr. Shorr. From my experience as a gynecologist I am in complete accord with Dr. Shorr's view that there is little danger of estrogens promoting the development of cancer. Perhaps we should have a few words on the psychiatric aspects of the menopause. Dr. Ripley, would you say something about that?

DR. HERBERT S. RIPLEY: Many women look upon the menopause as a period when their sexual life is on its way to the end or as a period of transition to the status of "old woman." In many the realization that the changes associated with aging are taking place is the cause of psychologic trauma. Inability to accept this fact is particularly manifest in women who have taken great pride in their youthfulness. These reactions result in the well known depressions associated with the menopause. There are two fairly distinct types. One is a mild reactive depression, probably a concomitant of the physiologic changes. These patients are helped on a regimen of replacement therapy which brings about improvement in the general condition of the individual. The second group represents more severe depressions of the manic depressive or involutional types. They occur at the time of the menopause and are associated with many vasomotor symptoms. In these replacement therapy may also be of considerable aid. The relief of the vasomotor symptoms brings about an increased sense of well-being, and the depression may become more bearable. In the involutional and manic depressive psychoses without vasomotor symptoms, however, little benefit is derived from estrogen therapy, for, contrary to the suggestion by several workers in this field, estrogen therapy is not specific for involutional melancholia. Dr. Shorr and I studied a group of patients of this kind a few years ago. We observed that cases of involutional or manic depressive psychoses often appeared beyond the menopausal age; women who had had the menopause at the age of forty-five often developed the depression at the age of sixty. Although such cases still fall into the psychiatric category of involutional psychoses, hormone therapy provided no appreciable relief. In fact several patients showed increase of symptoms due to intensification of sexual tension. One patient showed a very interesting reaction: delusional ideas which were related to the gastrointestinal tract shifted to the genital tract. This woman felt that her bowels were "clogged up" and never moved, but after treatment with estrogens she maintained that she had been impregnated by one of the physicians and was going to give birth to monkeys. When the hormone was discontinued, she returned to her preoccupation with her bowel. This brings us to the problem of the psychologic effects of estro-

gen hormones. Do they cause psychologic changes, and if they do, how constant or predictable are such reactions? We are a long way from an answer to this question. Studies have been carried out on the changes which may occur in women in relation to the amount of estrogenic hormone secreted. There is evidence that psychologic changes are associated with changes in the amount of female hormone circulating in the blood, but the changes are inconstant and show no uniformity. We are not in a position to state dogmatically that a particular psychologic state is induced in all women by a particular variation in hormonal or sexual activity. The psychologic factors are very complex and each case presents an individual problem.

DR. GAUSE: The menopausal patient is a very frequent visitor to the hospital clinic. Since the residents have a good deal to do with their treatment under these conditions, I should like to call on Dr. Thomas for a few words on his experiences.

DR. WILLIAM C. THOMAS, JR.: The majority of menopausal patients we see in the clinic have fairly severe symptoms. About one-half of them require some form of drug therapy. Most of us prescribe phenobarbital or some other mild sedative at the beginning and later resort to hormonal agents. I think we are all in agreement that the patient's personality and emotional problems present the most important and most difficult factors in treatment.

DR. HARRY GOLD: How much estrogen do you prescribe? What kind of routine do you follow?

DR. THOMAS: Our treatment is designed to give full estrogenic replacement. Dr. Shorr has established that most patients require between 2,000 and 4,000 rat units of an estrogenic preparation daily for this purpose. This dose is usually continued for two weeks and is followed by a one-week period of rest. We examine vaginal smears periodically to determine the effects.

DR. GOLD: How do you administer the hormones?

DR. THOMAS: We give them orally or parenterally. Preparations are available for both routes. We employ materials that have been standardized in terms of rat units. The standardization is carried out by both the oral and parenteral routes. The doses expressed in rat units refer to the oral or parenteral method of standardization, depending upon the route which is being used in the treatment of the particular patient. As I have stated, an attempt is made to use enough of the drug to establish full estrus, and it may take six weeks of treatment to reach that point. We determine the degree of symptomatic relief at this dosage level. We then reduce the dosage in steps, each new level being maintained for a period of three weeks. In that way we establish the minimal dosage required to maintain maximal relief.

DR. GAUSE: What do you mean by the "three-week periods"?

DR. THOMAS: The patient is maintained with a reduced dosage for two weeks followed with one week of rest. The dose is then again reduced, continued for two weeks and again followed with one week of rest. This system of reduction of the dosage is continued until the desired level is reached.

DR. GAUSE: Thank you, Dr. Thomas. Are there any questions for Dr. Shorr?

DR. GOLD: I should like to ask a question pertaining to the selection of preparations. The estrogen materials produce several effects, namely, changes in the smear, changes in the subjective symptoms and so on. One patient, for example, may suffer with severe headaches and another with severe flushes and sweats. Does the pattern or the spectrum of the action of different estrogenic materials differ? Is there any basis for the selection of estrogens in relation to these or any other manifestations of the menopause? Are some of the actions better developed in the molecular structure of one estrogen and other actions better developed in the structure of another estrogen? In relation to the adrenal cortical hormones it is well known that some exert a dominant action on sugar metabolism while others exert a greater action on the electrolytes.

Is there anything analogous to that in the case of the estrogens?

DR. SHORR: That is a very important point, Dr. Gold. Obviously, the best preparation would be one which could provide symptomatic relief without any biologic estrogenic effects, that is, endometrial proliferation, bleeding, etc. Reports have appeared from time to time suggesting that such a dissociation has been achieved in the case of a particular product. However, the fairly extensive experience which we have had in the use of the estrogens has convinced us that potency with respect to symptomatic relief runs parallel with potency as revealed by the vaginal smear. We have studied ten or twelve different preparations in considerable detail and the results leave us with little doubt that no one of the preparations possesses superiority in respect to the relief of symptoms over any other, which is not associated with parallel superiority in biologic potency. We believe that the choice of an estrogenic hormone in therapy should be made on the basis of cost, freedom from unpleasant side effects or toxic effects and ease of administration. Generally speaking, a natural estrogen the cost of which is sufficiently low to enable the patient to use the oral route would be the preparation of choice. The oral route is convenient; and when the daily requirement is taken in two doses, one in the morning and one in the evening, the efficiency of the dosage is increased. The reason why this is not usually done is the fact that estrogens are less effective after oral administration and to employ this route larger doses are required. Some natural estrogens are too costly to permit this.

DR. GOLD: Do you think all the natural estrogens are superior to the synthetic ones?

DR. SHORR: The advantage lies in the fact that the synthetic products are more active with respect to undesirable side effects and that some patients who require large doses can tolerate only the natural estrogens.

DR. GOLD: Dr. Shorr, would you briefly describe your routine for the use of estrogens in menopausal patients?

DR. SHORR: First, we give the estrogens in doses sufficient to return the vaginal smear to normal. This enables us to ascertain the extent to which the symptoms can be relieved by hormone therapy. We usually start with a dose equivalent to 1,000 rat units a day, by mouth or parenterally. If necessary the dose is increased to 2,000 or 3,000 units. These will produce the full effects in most patients although variations in requirements are very wide. I remember one woman in whom neither the normal vaginal smear nor relief of symptoms was possible with as much as 100,000 rat units a day. Such tolerance is, to be sure, exceptional.

After the normal smear has been obtained, treatment is discontinued and the patient is observed for the return of symptoms. Then treatment is usually resumed with the dose which during the first course provided the maximum degree of symptomatic relief. This may be smaller than the amount required for full replacement. In general we aim at the smallest dosage which provides the maximum degree of relief obtainable in the particular patient and then endeavor to maintain that state.

DR. GOLD: Why do you not refer to doses in terms of milligrams instead of "rat units"?

DR. SHORR: The reason is the fact that there is no correlation between the weight of different estrogens and their biologic activity. I know that the *U. S. Pharmacopeia* and the *New and Nonofficial Remedies of the Council on Pharmacy and Chemistry* have adopted the policy of expressing dosage of estrogens in terms of milligrams. I believe this was an unfortunate step for it has resulted in no end of confusion.

DR. GOLD: If you are going to express dosage in terms of the biologic unit, why do you employ the "rat unit" instead of the "U. S. P." or "International unit"?

DR. SHORR: The units by the two systems of assay are not comparable. For example, in the case of one compound the "rat unit" had the potency of one-third the "Inter-

national unit," while in the case of another compound the "rat unit" had the potency of one-eighth the "International unit." It is our belief that the results in terms of "rat units" are more dependable and are better correlated with the effects in humans.

DR. MCKEEN CATTELL: May I say a word in favor of discarding wherever possible the use of biologic units? Physicians must ultimately become familiar with the therapeutic dose of drugs in terms of weight or volume. Today no one would advocate expressing the dose of morphine, methadon, etc., in terms of analgesic units.

DR. GOLD: I should like to point out, Dr. Shorr, that the use of such a term as "rat unit" is no longer acceptable in pharmacology and by experts in bio-assay. The same applies to "mouse units," "pigeon units," "cat units" and all other animal units. The reason is that rats, mice, pigeons, cats and all other animals used in bio-assay show wide differences in susceptibility to a particular drug, with a great variety of factors. For example a so-called "cat unit" for a particular preparation of digitalis may show one value if the assay is carried out with cats which roam the streets of Chicago and a different value with cats collected from the sidewalks of New York. There is an endless variety of factors which influence the susceptibility of any species of animal to a particular drug. Pharmacologists, having recognized this point, have abandoned the principle of bio-assay in which the results are expressed in terms of the amount of drug required to produce the particular effect in a particular animal. In its place a different principle has been adopted, one in which the results will be free of the variables in the susceptibility of the animal. The new principle involves a comparison of the particular compound with a standard, using whatever the animal species happens to be, as the means for the comparison. This is the principle employed whenever possible in *U. S. Pharmacopeia* bio-assays. We therefore no longer say that the potency of a given compound is so many milligrams per kilogram of animal, but that the potency of the compound in question is equal to, or 50 per cent of, or 75 per cent of, the potency of a standard material with which the unknown is compared. Not all materials can be assayed in accordance with this principle because a standard is not available for the comparison in the case of all materials; but when there is a standard, no doubt remains that the most reliable information about the potency of an unknown is obtainable when it is compared with a standard. That is why I questioned your dependence on a "rat unit" as an expression of the potency of an estrogen in the place of a U. S. P. unit or an International unit.

There can be no question of the soundness of the point made by Dr. Cattell, namely, that drugs should be prescribed in terms of weight or volume rather than in terms of biologic units whenever possible. However, there is considerable evidence favoring the validity of the position taken by Dr. Shorr to the effect that the correlation between biologic activity and weight of material in the case of the estrogenic compounds is not sufficient to use these materials in terms of their weight. There is fairly strong indication that, for example, 1 mg. of each of two estrogens, which may produce equal effects by parenteral administration in the mouse or the rat, may produce effects which differ widely in their intensity when the two are compared by oral administration in humans. This may result from differences in the extent of their absorption and speed of elimination in the different species.

DR. GAUSE: Dr. Shorr, you stated that you prefer the oral route, but do not some patients require parenteral administration in order to obtain symptomatic relief?

DR. SHORR: I see no reason why the oral route cannot meet all the requirements.

DR. GAUSE: It is my experience, however, that some patients fail to obtain the same degree of symptomatic relief with the oral doses that they do with parenteral treatment.

DR. SHORR: This observation of yours may be explained by the psychologic factors which are introduced by an injection of a drug. These are important features, espe-

cially in those patients whose menopausal symptoms may be chiefly of psychic origin rather than the result of estrogen deficiency. Such patients may obtain relief from the injection of anything.

DR. JANET TRAVELL: Is there any oral preparation that you particularly prefer?

DR. SHORR: We commonly use premarin which is chiefly estrone sulfate although not completely pure. This is a natural hormone. It is not excessively costly; seven to ten cents for a tablet of 1.25 mg., equivalent to 800 rat units.

DR. NATHANIEL T. KWIT: When you use estrogens parenterally, what are the intervals between injections?

DR. SHORR: It varies a great deal. The more frequent the injection, the smaller is the dose required for a particular effect. The injection of 10,000 rat units once every ten days is a much less efficient way for using the drug than 500 rat units twice a day.

DR. GOLD: I assume that the reason for the low economy of the very large dose at one time is due to the losses by excretion of a large share of the material before there has been an opportunity for it to exert its action.

DR. SHORR: That is correct. When an excessive amount is given at one time, most of it is ineffectual, being inactivated chiefly in the liver. Estradiol, for example, is converted into estradiol glycuronate, which has only $\frac{1}{600}$ of the estrogenic activity of the original compound.

VISITOR: Dr. Ripley mentioned the increase in sexual tension which may occur in estrogen therapy. Is not libido generally increased in the menopause?

DR. RIPLEY: Occasionally it is, but most commonly sexual desires are reduced. Here again psychologic factors and the patient's personality influence symptomatology. A woman who has feared pregnancy and hence has rejected sexual activity may develop an increase in libido when she is aware of the fact that menopause has eliminated the possibility of becoming pregnant. However, the opposite is more generally true.

DR. ANNE C. CARTER: The androgens have an even greater effect on libido than the estrogens. They do not produce sexual desires in a woman who for psychologic reasons has never had them, but they will return libido to normal in those women in whom it was normal prior to menopause. This sexual effect is one of the factors limiting androgen therapy in women who have had no normal sexual outlet.

VISITOR: Will hormone therapy restore fertility?

DR. SHORR: I do not believe so. Intermittent therapy may produce periodic bleeding and this may lead the patient to believe she is again capable of becoming pregnant. There is the point that the menopause is not a static condition. During the menopause spontaneous return of fertility may occasionally take place. There is also the fact that fertility may not be abolished but only decreased, in which case pregnancy may be difficult but not impossible.

DR. GOLD: Do estrogenic materials differ sufficiently in their absorbability from the gastrointestinal tract to make one preferable to another? If 1,000 units of a preparation of which only 10 per cent is absorbed were to be given, it would produce much less effect than a similar dose of another preparation of which 50 per cent is absorbed. I ask this question because I have found it extremely difficult to come by information relating to this point from the clinical literature.

DR. SHORR: The absorption of estrogens varies widely. That is why we believe so firmly that oral preparations should be assayed in humans. That has been done for certain preparations. It is known that the natural estrogens are inactivated much more completely than the synthetic estrogens when given by mouth. For example estradiol, a natural estrogen, is inactivated to the extent of from 90 to 95 per cent while stilbestrol, a synthetic estrogen, is inactivated only about 50 per cent. Estradiol is marketed in terms of rat units. The unit for oral use represents ten times the amount of material in the intramuscular rat unit. The oral tablet which is labeled 600 oral rat

units contains an amount of compound represented by 6,000 rat units of the parenteral material. That should be done with every preparation.

DR. GOLD: I take it that the oral potency is not known for most preparations at the present time.

DR. SHORR: That is correct, and it is due largely to the fact that standards have been set up for expressing the potency in milligrams rather than in rat units.

DR. GOLD: It may be a fact that some physicians might find it less confusing to deal with dosage if they had to remember only one figure for both oral and parenteral dosage forms, for example, 600 rat units in the case of a particular preparation. If, instead, he used milligrams, he would have to remember two figures, one for the oral and the other for the intramuscular route. I wonder, however, whether there is not an advantage in calling a spade a spade; with the biologic unit system he comes to believe that the dose is the same by mouth and by intramuscular injection when in fact the dose is not the same since the manufacturer has put ten times as much material into the oral tablet as into the parenteral ampule; when the milligram system is used, there is no chance for the doctor being deceived about dosage since here he knows that the oral dose is much larger than the intramuscular one and he also knows how great this difference is. We must not confuse this problem with the problem of bio-assay and differences in potency of preparations.

DR. TRAVELL: Estrogens, then, present the same problems as preparations of liver. There are the units for oral administration and the units for injection. The dose may, for example, be 10 units in either case, but the different units are not the same, an oral unit containing much more of the potent material than the parenteral unit.

DR. SHORR: That is correct.

DR. GOLD: That method of dealing with liver preparations is justifiable because both the oral and the injectable materials are impure and are not available in forms suitable for expression in terms of milligrams. The case with the pure estrogens, however, is different, for they are available in pure crystal form and that makes it possible to express whatever amount is given by whatever route in terms of milligrams.

DR. ALEXANDER R. STEVENS, JR.: What proportion of patients who respond well to premarin would show equally satisfactory response to stilbestrol?

DR. SHORR: I do not have that information. I might cite the observation which we made some years ago in a study of stilbestrol in a group of patients in which some required small and others large doses. We found that among those requiring the large doses, between 25 and 40 per cent developed toxic symptoms. Whether stilbestrol can be substituted for the natural hormone depends on the dose which the patient needs for satisfactory therapeutic results. Among patients whose dosage requirement is small, it is probable that the incidence of satisfactory results will be as high with synthetic as with natural estrogens.

DR. WALTER MODELL: What is the dose of stilbestrol in terms of biologic units?

DR. SHORR: The estrus unit of stilbestrol is 1.5 to 3 mg. I should say that 1 mg. of stilbestrol given by mouth would be approximately equivalent to the effect of 1,200 rat units.

VISITOR: What dangers are there in the use of the estrogens?

DR. SHORR: The occurrence of permanent injury is not well established and is on the whole negligible. There are effects from overdosage, often unpleasant, such as disagreeable tenderness of the breasts, excessive endometrial hyperplasia and bleeding.

DR. CATTELL: Is it possible to prolong menopause by continuous therapy over long periods?

DR. SHORR: I do not think we can view it that way if what we are doing is to relieve the patient's symptoms. If the woman is enabled to cope with her anxieties and unpleasant life situations more effectively, the therapy should serve to shorten her period of disability.

DR. CATTELL: But do the physiologic adjustments of the menopause continue during the therapy?

DR. SHORR: I believe that treatment allows them to go on. In the intermittent form of therapy which was mentioned earlier, there is indication during the rest periods that adjustments are being made.

DR. GOLD: I have never heard of any systematic studies to compare the duration of the period of menopause in the treated and untreated patient. It might be difficult to determine with precision the beginning and ending. However, Dr. Cattell's question strikes me as a rather significant one. When the patient enters on the course of the menopause, mechanisms for bringing about adjustments are probably set in operation, and without proof to the contrary it would seem to me possible that the evolution of the whole process might be delayed by factors which control some of the disturbances and thereby reduce the stimulus to spontaneous adjustments. For example patients with anxiety states are often relieved by change to a less challenging environment; but although the patient enjoys considerable relief, there is indication that such change in the patient's life situations fails to accomplish any lasting results. They cannot learn how to deal with life's problems if they have been removed from exposure to them. I wonder whether there is not a good analogy to the effect of estrogens in possibly drawing out the evolution of the menopausal process. This, of course, has little to do with the practical question of whether or not estrogen therapy should be administered. Facts indicating that distressing symptoms are relieved and life is made more bearable provide a better basis for deciding that question.

STUDENT: You have mentioned the vaginal smear several times. Could you describe this procedure briefly?

DR. SHORR: It is really quite a simple procedure and one which deserves to be used more widely. Vaginal secretions are aspirated with a glass pipet, blown onto a slide, fixed in alcohol and ether, stained and the slide then examined in the microscope. A smear of a menopausal patient contains small round or oval cells with large nuclei which arise from the atrophic vaginal epithelium. In addition there are many leukocytes and much cellular débris. All this signifies a lack of estrogenic activity. When estrogens are given to such a patient, the cells grow, becoming large and flat with pyknotic nuclei. The leukocytes disappear. Eventually the smear resembles that of a normally menstruating woman. This indicates that the maximum effect of the estrogen has been obtained and further increases in the dose are unnecessary.

Most menopausal patients may, of course, be treated without recourse to the smear, but it is certainly useful in all and may be essential in those cases in which the cause of symptoms is in doubt.

DR. MODELL: Is there any essential difference in the treatment of the surgical menopause and the naturally occurring syndrome?

DR. SHORR: Surgical castrates, particularly younger patients, develop symptoms which tend to be more severe and last longer. Treatment is generally the same except for the fact that rest periods are not as essential and serve chiefly for the evaluation of symptoms. The treatment is continued for as long as these periods of evaluation indicate to be necessary. It may be one year or twenty years. Surgical removal of the uterus may actually make the therapy easier by eliminating the possibility of annoying uterine bleeding.

DR. GOLD: Is there danger of suppressing pituitary activity in relation to other endocrine organs by excessive doses of the estrogens? Is it possible that estrogens might, for example, inhibit the pituitary sufficiently to lead to hypothyroidism?

DR. SHORR: There is a reduction in pituitary gonadotrophic activity which follows the administration of estrogen, but we have no evidence that this is associated with parallel reductions in other pituitary functions. At least that has been our experience with menopausal patients. More severe dis-

turbances have been seen on rare occasions in the treatment of younger women. I remember one young woman in whom estrogen therapy markedly depressed pituitary activity. This was a case with reduced ovarian function, other severe endocrine abnormalities and advanced electrolyte disturbances suggesting Addison's disease. Such cases are rare and are not really related to the menopausal syndrome.

STUDENT: For how long after the last menstrual period may the patient continue to present symptoms due to the menopause?

DR. SHORR: I do not know the upper limits. I know that typical menopausal symptoms can occur in the mid-seventies, symptoms which can be relieved by estrogen therapy. There is an occasional interesting case in which the menopause *per se* is associated with no discomfort, but three or four years later, after a series of unsettling events which completely alter the life of the patient, a full-blown menopausal syndrome develops.

SUMMARY

DR. HARRY GOLD: Considerable ground was covered in this conference on the treatment of the menopause. The discussion involved both theoretic and practical issues and threw light on a large number of problems: Who is best equipped to treat the menopause; the relation between the symptoms of the menopause and the disturbance in hormones; the use of estrogens and androgens, and combinations of the two; estrogen therapy and cancer; the vaginal smear; the psychiatric disturbances of the menopause; the choice of preparations of estrogens, dosage and route of administration; natural versus synthetic estrogens; regimen for treatment; sources of confusion in the bio-assay of estrogens; and the question whether estrogen therapy prolongs the menopause.

The essential hormonal changes involve a urinary increase in gonadotrophic hormone of the pituitary and a marked reduction in circulating estrogen. Estrogen deficiency is the factor which appears to be related to the menopausal symptoms. The significance of the psychologic aspects of the menopausal syndrome was stressed from the standpoint of their role in the severity of the symptoms and the response to treatment. The patient's emotional and personal needs are considered more crucial than her medicinal needs. Nevertheless, substantial improvement may be anticipated from the appropriate use of the estrogens. Attention was called to the utility of these drugs in some cases of involutional depression related to the menopause, and signs to differentiate these from cases not likely to respond were given. The natural estrogens were preferred on the basis of the fact that when large doses are necessary they are less apt to produce disagreeable side effects than synthetic stilbestrol. It was pointed out that smaller doses at more frequent intervals are more effective than massive doses at very long intervals. The oral route was preferred and the belief was expressed that the alleged superiority of the parenteral route is due to the psychologic effect of an injection. The vaginal smear was described as an extremely valuable guide to estrogen therapy. A plan of intermittent treatment was outlined which insures that the full benefit of the drug is obtained. In this regimen the estrogen is administered until full replacement is observed in the smear. Then the dose is reduced by steps in the endeavor to establish the smallest dose which maintains the optimum state of improvement in menopausal symptoms. There appears to be no significant danger of cancer in the use of the estrogens for the treatment of the menopause. Attention was called to the need for pelvic examinations to insure that bleeding due to cancer unrelated to the treatment may not be mistaken for an effect of the estrogen.

Clinico-pathologic Conference

Aphasia, Hemiplegia and Cardiac Involvement

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, L. G. (No. 183221), was a white married farmer, sixty-four years of age, who entered the Barnes Hospital for the first time on April 8, 1950, complaining of inability to use his left arm and of difficulty in speaking. He was somewhat confused and unable to give an adequate history. Aside from the fact that his father had died at the age of fifty from heart disease, the family history was non-contributory. The past history revealed that the patient had enjoyed good health most of his life. When he was fifty-two, he developed persistent pain in the right upper quadrant which was completely relieved following cholecystectomy. For the last few years before entry he had been bothered by burning and frequency of urination and some decreasing vision. Twenty months prior to admission a small "mole," which had been present for several years, had been removed from the left cheek. Eleven months later it recurred and was again excised. Following the second excision the patient had noticed persistent drainage of watery material from the wound whenever he ate.

Two weeks prior to entry, while in the office of his oculist, the patient suddenly was unable to speak and his left arm became paralyzed. After several hours speech returned but subsequently the patient had difficulty in expressing himself clearly. He also regained some movement in his left arm but was unable to direct it to a given object. He had some difficulty in thinking clearly and two days after the episode noticed dizziness. These signs and symptoms persisted until he entered the Barnes Hospital.

At the time of entry, physical examination revealed the patient's temperature to be 36.8°C., pulse 72, respirations 18 and blood pressure 115/75. The patient was somewhat obtunded and was partially aphasic. He did not, however, appear acutely ill. The skin was scaly and dry, particularly on the extensor surfaces. No significant lymphadenopathy was noted. On the left side of his face, beneath the zygoma and anterior to the mandibular joint there was a yellow, scaly crust on a depressed region which measured 2 by 3 by 0.5 cm. in size. The edges about the depressions were raised and there was some surrounding erythema and edema. The lesion did not feel indurated. Bilateral purulent conjunctivitis was present. The pupils reacted normally although the left was somewhat irregular. The fundi were visualized poorly. Marked dental caries were noted. Examination of the chest revealed moderate emphysema, but the lungs were otherwise clear to percussion and auscultation. The heart was not enlarged. The sounds were distant and a grade 1 systolic precordial murmur was heard; the rhythm was regular, but there were frequent ventricular premature contractions. Examination of the abdomen revealed a well healed right upper quadrant scar. No organs or masses were felt. The prostate was normal to palpation, and no other abnormalities were noted on rectal examination. There was no edema. The peripheral arteries were thickened and tortuous but pulsated equally. The positive neurologic findings included mental dullness, confusion and partial aphasia. There was

definite left facial weakness of the central type and slight weakness of the left upper extremity with some spasticity. Definite astereognosis on the left was also noted. Sensory examination was inadequate because of the patient's inability to cooperate. His deep tendon reflexes were generally hyperactive, those on the left being more so than those on the right. The cremasteric reflex was absent on the left. Babinski signs were present bilaterally.

The laboratory data were as follows: Blood count: red cells, 4,610,000; hemoglobin, 15.2 gm.; white cells, 7,250; differential count, within normal limits. Urinalysis: negative. Blood Kahn test: negative. Non-protein nitrogen, 25 mg. per cent; sugar, 69 mg. per cent. The chest x-ray revealed only an old healed fracture of the right ninth rib. Skull films were negative. Electrocardiogram: T waves isoelectric in lead I, diphasic in V_4 and V_5, inverted in leads II, III, AVF and V_6. Interpretation: abnormal form of ventricular complex; question of ischemia of the posterior wall.

The patient was seen in consultation by a plastic surgeon who noted no evidence of recurrent tumor. There was a small fistula which drained saliva. After the pupils were dilated and the eye grounds again examined, revealing normal discs, a lumbar puncture was performed; the initial pressure was 150 and the final pressure 100 mm. of H_2O. The fluid was clear and contained 5 cells. The spinal fluid protein was 104 mg. per cent; the colloidal gold curve was flat and the Wassermann reaction negative. A second electrocardiogram revealed evidence of posterior lateral myocardial ischemia and a question of an old anteroseptal myocardial infarction. Ventricular premature contractions persisted. The patient's stay in the hospital was otherwise uneventful and he was discharged unimproved on April 18, 1950.

Following discharge the patient became progressively obtunded and then stuporous; incontinence of urine developed and he became a difficult nursing problem. He was readmitted to the Barnes Hospital on May 1, 1950.

Physical examination at the time of entry revealed his temperature to be 36.5°C., pulse 64, respirations 14 and blood pressure 110/70. The following changes from those noted on the previous admission were recorded: the patient was stuporous, appeared wasted and was cyanotic. His respirations were slow and shallow. All the extremities were more rigid and there was marked spasticity of the arms. The patient moved only his right side. There was complete loss of sphincter control.

The laboratory data were as follows: Blood count: red cells, 4,880,000; hemoglobin, 16.1 gm.; white cells, 16,800; differential count: myelocytes 1 per cent; stab forms 8 per cent; segmented forms 80 per cent; lymphocytes 9 per cent; monocytes 2 per cent. Urinalysis: albumin, 3 plus; sugar, negative; sediment, loaded with white and red blood cells. Stool examination: guaiac negative. Blood non-protein nitrogen, 45 mg. per cent; fasting sugar, 82 mg. per cent. Electrocardiogram: unchanged from previous admission.

The patient was placed in an oxygen tent and was given intravenous fluids. A Foley catheter was inserted and chemotherapy begun. Bloody urine passed through the Foley catheter. On the third hospital day the patient's respiration became increasingly slow and shallow, and both extremities became even more spastic. On the fourth hospital day his temperature rose to 38.5°C.; it remained above this level throughout the remainder of his course.

One week after entry the patient's condition was about the same although he responded to his name and was able to move his right arm and both legs slightly. The tendon reflexes continued to be hyperactive. Two weeks after entry a lumbar puncture was performed. The initial pressure was 250 mm. of water and 15 crenated red cells were found; the protein content was 94 mg. per cent. Because of his inability to take food by mouth the patient had to be maintained on parenteral alimentation until the third week when he became somewhat more alert and tube feedings were insti-

tuted. The cyanosis which had been present on entry disappeared and the patient was taken out of the oxygen tent. A urinalysis at this time showed 1 plus albuminuria and many white cells and bacteria in the sediment. A urine culture revealed pseudomonas aeruginosa.

During the last week of hospitalization there was no change in the patient's condition except that it was noted that his left leg had become cooler than the right; the arterial pulsations were equal. He developed a large decubitus ulcer and about the same time bleeding about the gums was noticed. His prothrombin time was found to be 46 per cent of normal and the nonprotein nitrogen 29 mg. per cent. The patient became comatose, his respirations became rapid and breath sounds were diminished over the right lower chest. Terminally his blood pressure fell, his temperature rose to 40°C. and he expired on June 14, 1950.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Our problem in reaching a diagnosis in this case is rendered more difficult by the fact that an adequate history could not be obtained from the patient at the time of his first admission. If we accept the information given us in the protocol, we must assume that the patient had enjoyed good health, except for mild urinary tract symptoms, until the onset of his neurologic complaints. It would seem to me very important to attempt to localize the site of his cerebral lesion. I should like to ask Dr. O'Leary whether he believes that this patient suffered from a diffuse or disseminated process or whether he believes a rather localized lesion would best explain the signs and symptoms.

DR. JAMES L. O'LEARY: It was not stated in the protocol whether this patient was right or left handed. I presume he was left handed.

DR. NORMAN KNOWLTON: There is a statement in the record that he was somewhat ambidextrous.

DR. O'LEARY: A certain amount of importance must be attached to the handedness in this case because when the patient developed the initial presenting signs in his oculist's office, he had weakness of the left arm and aphasia. I believe one could attribute the signs which he exhibited to a local lesion, either in the internal capsule of the right hemisphere or in the white matter between the pre- and post-central gyri on the right side. Later in the course other neurologic findings developed which suggested systemic involvement, but I believe I would at this point assume the patient had a local lesion, possibly thrombotic, but not necessarily so.

DR. ALEXANDER: Would a local lesion explain the bilateral Babinski signs?

DR. O'LEARY: I do not think the appearance of bilateral Babinski signs is out of the ordinary in a situation such as this.

DR. ALEXANDER: Later on he developed marked rigidity of both upper extremities along with incontinence and coma. Would those findings also still be in keeping with a local lesion?

DR. O'LEARY: No. The appearance of those additional signs suggest more diffuse involvement. I merely believe that the original presenting signs could have been explained by a single localized lesion. The subsequent signs could have arisen on the basis of cerebral vascular disease, however.

DR. ALEXANDER: The history is not very clear about the patient's present illness; but if it had arisen on the basis of a vascular lesion, would you not have expected it to be more gradual in onset?

DR. O'LEARY: Not necessarily so.

DR. ALEXANDER: In other words, one may assume that a patient might develop a very sudden hemiplegia, such as this patient did, and then exhibit the type of course he did on the basis of a vascular lesion.

DR. O'LEARY: I believe, in view of his age, that the entire picture is compatible with cerebral vascular disease. I agree that there are certain other factors which must be considered, but the entire history seems to me to fit in perfectly well with vascular disease.

DR. ALEXANDER: What about the high spinal fluid protein? Is it in keeping with the diagnosis of cerebral thrombosis?

DR. O'LEARY: No, I believe that is an important point which might well lead me away from that diagnosis. Further, the presence of a small number of crenated red cells at the time of the second lumbar puncture and the higher spinal fluid pressure also would be against my original diagnosis.

DR. ALEXANDER: If this were cerebral thrombosis, and as Dr. O'Leary points out it could be, one would have to assume that the patient had extensive cerebral arterial disease. That would be compatible with the fact that his peripheral arteries were tortuous, and with the observation on repeated electrocardiograms of evidence of severe cardiac involvement. Dr. Levy, what other diagnoses should be discussed?

DR. IRWIN LEVY: I think an embolic process should also be considered.

DR. ALEXANDER: It is perhaps in keeping with that diagnosis that the patient's urine, which on the first admission was entirely negative, showed many red cells in addition to white cells during his second admission. It is conceivable that the microscopic hematuria arose on the basis of embolic phenomena. If so, where might the emboli have arisen?

DR. SEDGWICK MEAD: From the left ventricular wall.

DR. ALEXANDER: Although the patient's heart was not enlarged on x-ray, it probably was the site of significant pathologic change, and it would be interesting to inquire as to whether the changes were acute. Dr. Paine would you discuss the electrocardiograms?

DR. ROBERT PAINE: The first electrocardiogram showed changes over the posterior and apical portions of the heart. The T waves were inverted in leads II, III, AVF, V_6, V_7, and V_8. Such T wave inversion is indicative of abnormal myocardial metabolism and is most often associated with myocardial ischemia. Other myocardial metabolic disturbances could have produced these changes, however. The tracing taken on the second admission showed marked changes from the previous tracing. The T waves were upright in leads II, III and AVF and inverted in AVL, V_1, V_2, V_3, V_4, V_5 and V_6. There was a deep Q wave in V_1, V_2, and V_3. These changes suggest anterior myocardial disturbance and have the same significance as the previous posterior abnormalities; that is, they probably represent myocardial metabolic dysfunction. In the third electrocardiogram taken one day after the second the T waves were upright in V_1, V_2 and V_3 and less inverted in V_4, V_5 and V_6. These changes are more toward normal. Their evolution suggests a rapidly changing state of ischemia in the anterior myocardium. These three records, therefore, show an undulating course with a disturbance first in the posterior myocardium and later in the anterior myocardium.

DR. EDWARD H. REINHARD: Dr. Alexander, could we ask Dr. Paine whether there is anything in these electrocardiograms which would not be consistent with a metastatic process to the myocardium rather than to myocardial infarction *per se?*

DR. PAINE: The changes here are indicative only of damage to the myocardial fibers, and give no clue as to the nature of the process causing the damage.

DR. ALEXANDER: Do you believe that the changes are consistent with an acute myocardial infarction, Dr. Paine?

DR. PAINE: They are compatible with but not diagnostic of an acute myocardial infarction.

DR. ALEXANDER: Dr. Smith, is it possible that this patient may have had an acute infarction of the heart with the formation of a mural thrombus in the cavity of the left ventricle and subsequent embolization of a part of the thrombus to the brain?

DR. JOHN R. SMITH: That suggestion is entirely possible. As far as we know from the limited history, this patient did not have pain suggestive of myocardial infarction. On the other hand, it should be pointed out that in some series as many as 50 per cent of patients with proven myocardial infarction gave no history of chest pain or any of

the other signs or symptoms of myocardial infarction except the electrocardiographic changes. Therefore, your postulate is perfectly tenable. This particular problem arises not infrequently and is a most difficult one.

DR. ALEXANDER: Is embolization to the brain as a result of mural thrombi at the site of an infarct common? Does it occur as frequently as does embolization to the peripheral arteries?

DR. SMITH: It is certainly not uncommon although it is not seen as often as is embolization to the other parts of the body. The situation is analogous to that which obtains in subacute bacterial endocarditis in which embolic phenomena may involve any portion of the body.

DR. ALEXANDER: This patient had evidence of a urinary tract infection with fever, leukocytosis and many white cells in the urinary sediment. Dr. Harford, would you comment on this aspect of the problem?

DR. CARL G. HARFORD: I believe it most likely that the urinary infection was secondary; it probably developed as a consequence of the use of the retention catheter.

DR. ALEXANDER: Do you believe the clinical picture is compatible with encephalitis?

DR. HARFORD: I believe that the diagnosis of encephalitis would be most unlikely here, but it is always very difficult to rule out completely.

DR. ALEXANDER: Dr. Levy would you consider any other possibilities?

DR. LEVY: In regard to emboli one must always think of the possibility of the abscess formation at the site of the embolus. The signs which developed later in this patient's course suggest a space-taking lesion and an abscess should be considered in that regard.

DR. REINHARD: I think one possibility which we should mention at this time revolves around the "mole" which was removed from the patient's face. That lesion, which apparently had been present for several years, makes me think of malignant melanoma. Within a year after the removal of the lesion, the patient developed bizarre neurologic signs and died; it would seem to me that the burden of proof is on him who says that the patient did not have malignant melanoma. It is important to point out that this particular tumor develops rapidly and metastasizes more widely than almost any other tumor known. Particularly of interest here is the fact that Dr. Ackerman, in a series which he collected at the State Cancer Hospital, found that 50 per cent of the patients dying of malignant melanoma had metastases to the heart.[1] Classically, the tumor also involves the central nervous system, and often other organs which are infrequently the site of metastases with other tumors, for example, the spleen.

DR. ALEXANDER: Your suggestion is a very important one. The original lesion was excised about twenty months before the patient came to the hospital. When he was seen here by a very competent plastic surgeon, no local evidence of recurrent melanoma was noted. Would that be compatible with the course of malignant melanoma which has metastasized?

DR. REINHARD: Certainly the tumor may appear elsewhere without recurring locally.

DR. ALEXANDER: Just before the conference began Dr. Levy told me he believed this patient had malignant melanoma. I should like to ask him why he thinks so.

DR. LEVY: As I have indicated, I believe that the terminal course was compatible with a space-taking lesion. Furthermore, the elevated spinal fluid pressure also suggests a mass in the brain.

DR. ALEXANDER: Dr. Schwartz, would you care to comment?

DR. HENRY G. SCHWARTZ: I would agree that melanoma is the most likely possibility to explain the entire picture. It was my belief that the primary symptomatology which he exhibited could be explained on the basis of a lesion involving the cortex or compressing the cortex on the right side, leading to astereognosis. I say that because astereognosis was mentioned without mention of loss of pain or other sensory modalities. Usually astereognosis without the loss of

[1] ACKERMAN, L. V. Malignant melanoma of the skin. *Am. J. Clin. Path.*, 18: 602, 1948.

other sensation places a lesion in or near the cortex. Subsequently the patient developed the clinical picture of diffuse central nervous system involvement which leads me to believe that tumor, in and over the cortex, spreading later through the subarachnoid space, was responsible for the whole picture.

DR. ALEXANDER: You would think that such a process could explain the high spinal fluid protein?

DR. SCHWARTZ: Yes.

DR. REINHARD: This patient's urine on the second admission showed a large number of red blood cells. One wonders whether the patient also may not have had metastatic lesions in the kidney. As I have pointed out this particular tumor metastasizes very widely and explosively.

DR. W. BARRY WOOD, JR.: Apparently during the patient's hospital stay the diagnosis of metastatic melanoma was not considered seriously. Had it been, a test for melanin in the urine might have been performed. How valuable is that test, Dr. Dammin?

DR. GUSTAVE J. DAMMIN: In the patients studied by Dr. Ackerman approximately one-third had melanin in the urine.

DR. O'LEARY: Would Dr. Moore tell us how commonly malignant melanoma occurs on the face as compared to other areas of the body?

DR. ROBERT A. MOORE: About a third of malignant melanomas occur on the head and neck.

DR. ALEXANDER: Is there a primary melanoma of the central nervous system?

DR. LEVY: Yes there is. It occurs usually in the spinal cord and cauda equina.

DR. ALEXANDER: In summary then, a number of diagnoses have been suggested to explain the clinical picture which this patient exhibited. Among them have been: cerebral vascular disease, presumably on an arteriosclerotic basis; cerebral embolization, secondary to mural thrombi at the site of a myocardial infarction; and finally, metastatic melanoma with involvement of both the brain, heart and possibly the kidneys.

Clinical Diagnoses: ? Cerebral vascular disease; ? myocardial infarction, mural thrombi and emboli to the brain; ? malignant melanoma of the face, metastatic to the brain, heart and kidneys.

PATHOLOGIC DISCUSSION

DR. DALE M. SCHULZ: External examination revealed a depressed atrophic scar 4 cm. in diameter on the left side of the face. The serous cavities contained no excess fluid; the pericardial cavity was obliterated by loose fibrous adhesions. The heart weighed 340 gm. On its external surface, along the course of the right coronary artery, there were three nodules of brownish black tissue measuring 3, 6 and 30 mm. in diameter, respectively. The largest nodule located near the apex surrounded the terminal branches of the artery but did not restrict the lumens. This nodule extended 20 mm. into the posterior portion of the interventricular septum. Several small nodules of similar black tissue were attached to the endocardial surface of the right ventricle. The coronary arteries contained no arteriosclerotic lesions.

The lungs were heavy, weighing 1,800 gm. and were subcrepitant. The pleural surfaces showed alternating, depressed, blue areas of atelectasis and pink, aeriated regions. Poorly defined, irregular, nodular foci of increased resistance were felt in all lobes. The cut surfaces exuded foamy fluid which was grey and turbid. Some of the small bronchi contained similar fluid. In both lower lobes there were masses of firm grey tumor tissue, measuring 1 by 2 cm. in cross section, which extended through the visceral pleura and were attached to the parietal pleura. Several mediastinal lymph nodes were enlarged and greenish black in cross section.

The liver weighed 1,750 gm. and contained many nodules 3 to 15 mm. in diameter, some of which were brownish black while others were yellowish white. The kidneys weighed 160 gm. each and contained several small (3 to 8 mm.) black nodules. At the lower pole of the left kidney there were several pyramidal foci of yellow-

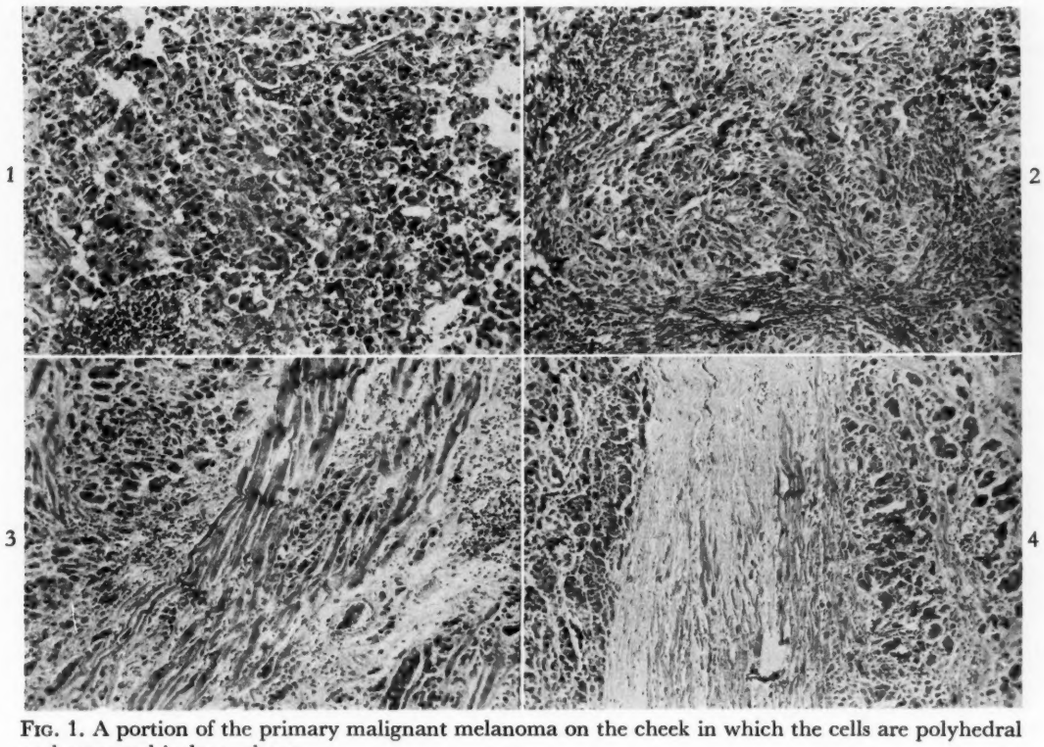

FIG. 1. A portion of the primary malignant melanoma on the cheek in which the cells are polyhedral and arranged in loose sheets.
FIG. 2. Loose whorls of irregular fusiform cells in another area from the primary tumor.
FIG. 3. Metastatic malignant melanoma in the myocardium with accompanying fibrosis and a lymphocytic infiltrate but no evidence of damage to the myocardial fibers.
FIG. 4. A broad band of fibrous tissue, containing isolated myocardial fibers, in association with metastatic tumor in the heart.

ish tissue surrounded by narrow zones of hemorrhage. Each adrenal gland contained a 1 cm. nodule of greenish black tissue. The spleen weighed 160 gm. and was not unusual.

Scattered over the surface of the brain and throughout the substance of the cerebrum, cerebellum and pons were scores of brownish black nodules of tumor that varied from 5 to 30 mm. in diameter. Nodules were present in the right motor cortex as well as in the temporal lobe and adjacent to the internal capsule. Those at the periphery of the brain bulged slightly above the surrounding surface. No skeletal metastases were seen grossly but tumor was detected in a rib by radiologic examination.

DR. ROBERT A. MOORE: The diagnosis of metastatic malignant melanoma of the heart, brain, lungs, kidneys and many different lymph nodes and other organs throughout the body was obvious from the gross appearance of the scattered pigmented tumors. At the time of the autopsy none of these tumors was in likely sites or of the appearance of a primary malignant melanoma; however, microscopic slides of the mole removed from this patient's cheek two years before his death were obtained. The first two illustrations are of that tumor which was clearly the primary malignant melanoma. In Figure 1 there are loose sheets of large polyhedral cells characteristic of a melanoma. Within these cells there were often brown granules of melanin and many mitotic figures could be seen. The histologic pattern of the tumor, even within the primary, was not uniform but varied from field to field. In another area (Fig. 2) the cells were more fusiform and were arranged in indistinct whorls or bundles. Such a variation in histologic appearance is characteristic of malignant melanomas as a class and in this case was well illustrated not only in the primary tumor but in the various metastases.

From its gross appearance it was obvi-

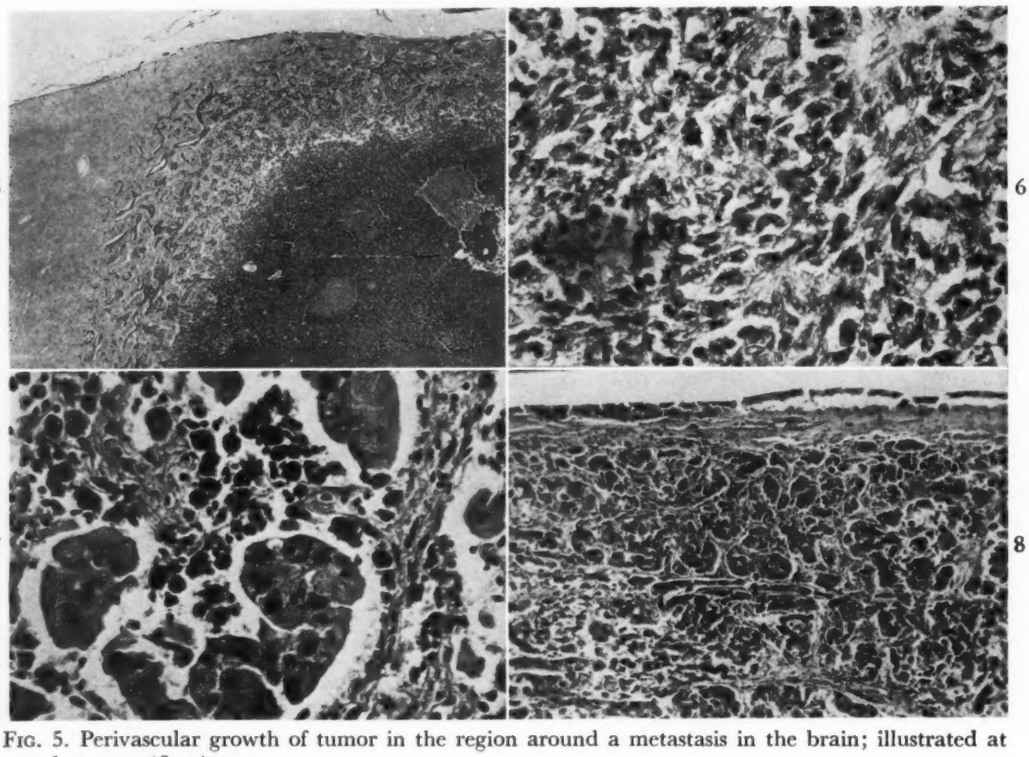

FIG. 5. Perivascular growth of tumor in the region around a metastasis in the brain; illustrated at very low magnification.
FIG. 6. Spindle-formed cells of tumor in a cerebral metastasis.
FIG. 7. Cytoplasmic granules of melanin in cells of the metastasis in the liver.
FIG. 8. Polyhedral cells in an alveolar arrangement from a subpleural metastasis.

ous the myocardium contained metastatic tumor, particularly a nodule about 3 cm. in diameter in the posterior portion of the septum. Figure 3 illustrates the character of these metastases. In them there are masses of tumor cells in small groups which have infiltrated between myocardial fibers and which are accompanied by slight fibrosis and an infiltrate of lymphocytes. Myocardial fibers are well preserved and nowhere is there any necrosis. Figure 4 shows that in some areas the fibrosis that accompanied the tumor is extensive and has isolated individual myocardial fibers. The alveolar pattern of the tumor in this site also illustrates another facet of its pleomorphism. Because of the changes in the electrocardiogram observed during the patient's stay in the hospital, we made an effort to decide whether there had ever been an infarct present in this heart. Certainly none was recognizable grossly; however, there was a possibility that one might have been masked by the overgrowth of metastatic tumor. Such seemed unlikely as there was no arteriosclerosis of the coronary arteries or other evidence of their obstruction, there was no necrosis of myocardial fibers, and the type and degree of the fibrosis noted indicated that it was primarily associated with the tumor. We have, therefore, concluded that there was no actual infarct, but that the heart was involved by an expanding tumor that caused a certain amount of fibrous tissue reaction around and in the tumor and resulted in the changes in the physiologic function of the myocardium reflected in the electrocardiogram.

In the brain (Fig. 5) there was an interesting invasion and growth of tumor in the Virchow-Robin spaces for considerable distances about the metastatic nodules; and in that site, more than in the metastases in the viscera, the cells were of a distinct spindle shape. (Fig. 6.) There were sufficient nodules at various specific sites to explain all of the observed neurologic

findings. Some of the metastases projected from the surface of the brain. We did not observe involvement of the skull.

In Figure 7 some large polyhedral cells of a metastasis in the liver can be seen to contain cytoplasmic granules typical of melanin. A final example of the varied architecture of this tumor is shown in Figure 8 which represents a subpleural nodule from the lung. Here the tumor is composed of polyhedral cells in a distinct alveolar arrangement. Sections from elsewhere in the lungs showed an intense bronchopneumonia from which Staphylococcus aureus had been obtained by culture at autopsy. Sections of the lesions in the lower poles of the kidneys revealed infarcts unassociated with metastases of tumor. These lesions, especially the larger one on the left, supplied an adequate explanation for the hematuria observed during life.

In summary, this man had a malignant melanoma of the cheek which was removed about two years before his death and which recurred at the site of excision eleven months later; it was removed a second time and did not recur. There was, nevertheless, extensive dissemination of the tumor to various viscera; practically all the symptoms of his terminal illness were related to metastatic tumor in various organs, especially in the brain and heart. In view of the primary diagnosis the outcome of this case could be called typical. Macdonald,[2] for instance, has reported a five-year survival rate of only 17 per cent in a series of 149 cases of malignant melanomas of the skin. The primary location of 32 per cent of these tumors is on the head and neck.[1] The heart is a site of metastasis of malignant tumors in general in only 7.3 per cent of such cases but is involved in over 50 per cent of metastasizing melanomas; however, it should be recognized that carcinoma of the bronchus is six times as frequently the source of metastatic tumors in the heart as is melanoma due to the relative incidences of the two primary tumors.[3]

Anatomic Diagnoses: Metastatic malignant melanoma in the brain, heart, liver, lungs, kidneys, pancreas, adrenal glands and the mediastinal and periaortic lymph nodes; atrophic scar on the left cheek; infarct in the left kidney; bronchopneumonia of all lobes of the lungs.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

[2] Macdonald, E. J. Malignant melanoma in Connecticut, pp. 71–81 in Miner, R. W. The Biology of Melanomas Vol. 4. New York, 1948. Special Publications of the New York Academy of Sciences.

[3] Scott, R. W. and Garvin, C. F. Tumors of the heart and pericardium. *Am. Heart J.*, 17: 431, 1939.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE WESTERN SECTIONAL MEETING IN SALT LAKE CITY, UTAH, JANUARY 26, 1950

EFFECT OF SYMPATHETIC DENERVATION ON GASTRIC SECRETION AND ON GASTROINTESTINAL TONE AND MOTILITY.

Alvin R. Kraus, M.D. and Theodore B. Massell, M.D., Van Nuys, Calif. (From the Vascular Surgery Section, Birmingham Veterans Administration Hospital.)

Although the effects of parasympathetic denervation of the human stomach are well known little information is available on the influence of sympathectomy. The purpose of this study was to determine the effect of sympathetic denervation on gastric secretion, gastrointestinal tone and motility, and thus to determine whether such denervation increases the tendency toward peptic ulcer formation.

Bilateral thoracolumbar sympathectomy and splanchnicectomy was performed on twelve patients for essential hypertension. In two patients vagotomy was done for duodenal ulcer, in addition to sympathectomy. Laboratory studies consisted of twelve-hour night gastric secretion, gastric analyses with test meal and histamine stimulation for free hydrochloric acid and barium meal x-rays for gastrointestinal motility. Results are given in the following table:

EFFECT OF SYMPATHECTOMY

	Normal or Unchanged	Increased	Decreased
Free HCl with meal and histamine	1	3	*8
12 hr. night secretion	2	5	*5
Gastric tonus	5	1	*6
Gastric motility	8	2	*2

* Includes the two patients in whom vagotomy was done simultaneously with sympathectomy.

Although these results represent the early effects, there is no indication that the tendency toward peptic ulcer formation is influenced by sympathetic denervation of the gastrointestinal tract. Further observation is warranted.

EFFECT OF ACTH ON SULFUR METABOLISM.

Sheldon Margen, M.D., Maxine E. Hutchin, M.D., Judith M. Lange, M.D., Harold Tarver, M.D., George D. Michaels, M.D. and Laurance W. Kinsell, M.D. (From the Metabolic Research Unit, United States Naval Hospital-University of California; the Dept. of Biochemistry, University of California, and the Division of Medicine, University of California Medical School, Oakland, Berkeley and San Francisco, Calif.

The administration of ACTH (peptide mixture and whole ACTH (Li)) to a patient on chemically constant dietary intake resulted in a marked increase in total urinary sulfate and urinary organic sulfur. Prior to ACTH administration approximately 30 per cent of the urinary organic sulfur was identified as methionine and cystine-cysteine-glutathione sulfur. The remaining 70 per cent is still unidentified. The proportion of these components remained roughly the same during ACTH administration.

URINARY EXCRETION OF LABELED AND NON-LABELED SULFUR AFTER ADMINISTRATION OF ACTH AND TESTOSTERONE PROPIONATE

Urinary Constituents	ACTH	Testosterone Propionate
Total sulfate (non-labeled)	Increased	Decreased
Organic sulfur (non-labeled)	Increased	Decreased
$S^{35}O_4$	Increased	No change
Organic S^{35}	No change	Increased

Studies also were carried out with tracer doses of S^{35}-labeled-methionine. The administration of the ACTH peptide caused a marked increase in $S^{35}O_4$ excretion, but no increase in *labeled* organic sulfur, despite the large increase in *non-labeled* organic sulfur. These findings are in contrast to those noted during testosterone propionate administration as seen in the preceding table.

EFFECT OF ACTH AND CORTISONE UPON THE ARTHUS RESPONSE IN GUINEA PIGS HYPERSENSITIVE TO PROTEIN ANTIGEN (EGG ALBUMEN). *Marcus A. Krupp, M.D., Ephraim P. Engleman, M.D. and Fred I. Gilbert, M.D., San Francisco, Calif.* (From the Veterans Administration Hospital and Stanford University School of Medicine, and Division of Medicine, University of California School of Medicine.)

Guinea pigs were sensitized to crystalline egg albumen injected subcutaneously at two-week intervals. After the second and third injection the effects of ACTH and Cortisone were measured upon dermal reactions following intracutaneous injection of the ovalbumin antigen.

Group	No. of Animals	Dermal Reaction (Arthus Type)	
		6 Hr.	24 Hr.
1. Unsensitized controls	5	All negative	All negative
2. Sensitized controls	7	6 Positive	6 Positive, fading
		1 Negative	1 Negative
3. ACTH, 2.5 mg. i. p. every 6 hr. for 24 hr. prior to and 24 hr. after skin test		9 Negative	9 Negative
		1 Positive	1 Positive, fading
4. Cortisone, 10 mg. in 2 cc. vehicle subcutaneously 24 hr. prior to and 15 min. prior to skin test	10	8 Negative	8 Negative
		2 Positive	2 Positive, fading
5. Vehicle (free of Cortisone) subcutaneously 24 hr. prior to and 15 min. prior to skin test	5	3 Positive	3 Positive, fading
		2 Negative	2 Negative

It is evident that in ovalbumin-sensitized guinea pigs ACTH and Cortisone prevent or modify the cutaneous reaction following intracutaneous injection of the antigen.

EFFECTS OF ACTH IN CHRONIC NON-GRANULOMATOUS IRIDOCYCLITIS. *Ephraim P. Engleman, M.D., Marcus A. Krupp, M.D., Max Fine, M.D., Michael J. Hogan, M.D., Laurance W. Kinsell, M.D., Malcolm R. Miller, M.D., Peter Kunkel, M.D. and Sheldon Margen, M.D.* (From the Medical Service of the San Francisco Veterans Administration Hospital, Divisions of Medicine and Ophthalmology, University of California School of Medicine, Stanford University Medical School and the Metabolic Research Unit of the University of California, U.S. Naval Hospital, San Francisco and Oakland, Calif.)

Three cases of chronic iridocyclitis associated with rheumatoid arthritis were treated with ACTH for 24, 50 and 100 days, respectively. Several days after the appearance of adrenal cortical stimulation and the expected improvement in the arthritis, changes in the eyes occurred, especially in the anterior chamber and vitreous. In the anterior chamber, ACTH caused the reduction of cells, flare and keratic precipitate. In the vitreous, opacities decreased resulting in improved vision and better visualization of the fundi.

In the one case in which ACTH has been discontinued, relapse of eye manifestations has occurred paralleling the relapse of the arthritis. It is apparent that the eye affords unique opportunity to visualize the effects of ACTH on inflammation.

LABORATORY AND CLINICAL OBSERVATIONS ON POLYMYXIN B AND E. *E. Jawetz, M. D., San Francisco, Calif.* (From the Divisions of Bacteriology and Pediatrics, University of California Medical School.)

The polymyxins are stable peptides derived from B. polymyxa with marked antibiotic action on gram-negative bacilli. *In vitro* the polymyxins are rapidly bactericidal, and resistant bacterial variants arise infrequently. Of the gram-negative bacteria frequently resistant to other chemotherapeutic agents A. aerogenes and Ps. aeruginosa are often susceptible to the polymyxins while proteus is usually resistant.

Polymyxin administered intramuscularly to patients was excreted slowly in the urine. Drug accumulation was marked if the dose exceeded 3 mg./kg./day or if renal function was impaired. Most satisfactory results were obtained with intramuscular injection of 1 mg./kg. every twelve hours. For topical administration solutions of 1 mg./ml. of polymyxin in saline were used.

In acute and subacute infections of the urinary tract with Ps. aeruginosa and other gram-negative bacilli not responding to chemotherapy polymyxin gave excellent results. It not only

suppressed the infective organisms but frequently sterilized the urine permanently. Topically applied polymyxin rapidly eliminated the organisms in infections of wounds or mucous membrane lesions with Ps. aeruginosa.

Toxic side effects limited the widespread use of the polymyxins in their present form. The nephrotoxic action was a function of dose and length of administration. It was negligible with 2 mg./kg./day polymyxin administered for seven days or less. The neurotoxic action produced impressive but transient paresthesias, dizziness, ataxia and weakness. Nevertheless, used with proper caution the polymyxins are at present the best drugs for the control of some infections due to resistant gram-negative bacilli, particularly Ps. aeruginosa.

STUDIES ON THE CLINICAL PHARMACOLOGY OF AUREOMYCIN. *Henry Brainerd, M.D., Henry Bruyn, M.D., Gordon Meiklejohn, M.D. and Louis O'Gara, M.D., San Francisco, Calif.* (From the Infectious Disease Laboratory, San Francisco Hospital, and the Divisions of Medicine and Pediatrics, University of California School of Medicine.)

A serial tube-dilution method of assay was used to study the absorption, distribution and excretion of aureomycin. The sensitivity to aureomycin of 109 bacterial strains was determined by a similar method. Most sensitive were gram-positive cocci. Most gram-negative rods were somewhat less sensitive. Proteus and pseudomonas were usually resistant.

Serum concentrations following single oral doses of 250 mg. and 1 gm. were similar for four hours. Appreciable concentrations persisted beyond six hours following the 1 gm. dose, causing accumulation in the serum if this dose was repeated every four to six hours. Serum levels at six hours were much lower following the 250 mg. dose. Intravenous administration of 50 to 100 mg. produced serum concentrations lasting six hours or more. Intramuscular administration rarely produced measurable absorption. Absorption following rectal administration or aerosolization was inconsistent.

Diffusion of aureomycin into cerebrospinal, pleural and joint fluids was irregular and often delayed. Aureomycin appeared in the bile of one of two subjects tested.

Urinary excretion was impossible to measure accurately because of the rapid deterioration of aureomycin in concentrations of less than 100 μ/ml. in the urine but excretion appeared prolonged. Antibacterial activity was detectable in the stools of individuals receiving aureomycin by mouth.

INFLUENCE OF SC1950 ON PERIPHERAL BLOOD FLOW IN HEALTH AND DISEASE. *Paul Yamauchi, M.D., R. E. Morrison, M.D., B. O. Kondo, M.D. and Travis Winsor, M.D., Los Angeles, Calif.* (From the Nash Cardiovascular Foundation, Hospital of the Good Samaritan and the Department of Medicine, University of Southern California Medical School.)

There is considerable need for vasodilating agents which are capable of reducing peripheral resistance, thereby increasing the rate of blood flow to the extremities. The drug SC1950 (quaternary amine) was selected for study as it has been shown that this drug successfully blocks autonomic ganglia in animals and man. Blood pressure is lowered and intestinal motility is considerably retarded. Blood pressure, pulse rate, amplitude of pulsation of a digit or limb and blood flow of a digit were recorded simultaneously employing the venous occlusion technic in five rabbits and fifteen subjects. Of the subjects, three were normal, two had essential benign hypertension and the remainder had arteriosclerosis obliterans of the peripheral arteries. In animals and man the systolic and diastolic blood pressures fell promptly and often drastically, with a gradual return to normal. The cardiac rate was occasionally accelerated, but more often was unchanged, probably indicating paralysis of the cardiac accelerating mechanism. Coincident with or shortly after the fall in blood pressure the peripheral blood flow was increased often markedly in animals and man. The increased flow to the periphery was considerably less in diseased patients than in normal individuals. The drug was not epinephrine-reversing as epinephrine given after SC1950 reduced the skin temperature and blood flow and increased the arterial pressure. The peripheral action of the drug was not blocked by atropine, indicating that the vasodilation was not due to parasympathetic stimulation.

STUDIES OF SKIN TEMPERATURE AND OF INDIRECT VASODILATATION IN AMPUTATION STUMPS. *Ellen Brown, M.D. and Nadine Foreman, M.D., San Francisco, Calif.* (From the Division of Medicine and the Prosthetic Devices Research

Project, University of California School of Medicine.)

Evaluation of the status of the circulation in amputation stumps has been undertaken in conjunction with studies concerning stump and phantom limb pain. In nine amputees (six lower limb, three upper limb), skin temperature of the four extremities was measured by thermocouples attached to the ends of the digits or of stumps, and at symmetrical points along the limbs. Room temperature was maintained between 18° and 21°C. Skin temperatures were recorded (1) during a cooling period in which the body was uncovered and (2) while the trunk and proximal portions of two or three extremities were wrapped in an electric blanket after administration of 30 to 60 cc. of whiskey.

After one and one-half to two hours cooling, temperature at the end of the stump was always lower than at the corresponding point on the contralateral extremity, and in the stump the proximal distal fall of temperature per unit distance along the limb was increased.

Following heat and alcohol, skin temperature in the normal extremities rose to levels indicating full vasodilatation, but stump temperature failed to rise in all except three subjects. These three amputees in whom partial or complete vasodilatation occurred were all wearers of suction socket prostheses.

Experiments using sympatholytic drugs and procaine injection of sympathetic ganglia showed essentially similar results.

No correlation has been found as yet between the severity of phantom pain and the ability of stump temperature to rise during body warming or following drugs.

TREATMENT OF HYPERTENSION WITH A 350 MILLIGRAM SODIUM DIET. THE ROLE OF PATIENT COOPERATION. *Benjamin Shorr, M.D. and Maurice Sokolow, M.D., San Francisco, Calif.*

Observations were made on ninety unselected, ambulatory patients with essential hypertension who attempted to remain on a 350 mg. sodium diet for at least six months. None had cardiac failure. Forty patients abandoned the diet after a short trial; fifty presumably remained on the prescribed diet.

A control period of observation preceded the dietary regimen. Serial electrocardiograms, chest films and renal function studies were made in addition to clinical studies. Dietary adherence, as determined by frequent sodium assays of twenty-four-hour urine collections, was excellent in fifteen patients, good in twelve, fair in eleven and poor in twelve.

Of the fifteen patients whose dietary adherence was continuous and excellent (less than 1 gm. of sodium excreted in twenty-four-hour urine specimens), six showed objective improvement, seven showed no change and in two the disease progressed. Thirty-five subjects showed electrocardiographic evidence of improvement. The cardiac size decreased in three patients. Papilledema disappeared in two patients; in one other hemorrhages and exudate decreased. In one patient, a significant decrease in blood pressure occurred.

Of the thirty-five less cooperative patients only two showed objective improvement, twenty-four remained stationary and in nine the disease progressed unfavorably. No objective improvement was seen in patients whose excretion of sodium exceeded 3 gm. daily, indicating failure to remain on the diet.

INTRA-ARTERIAL CATHETERIZATION IN MAN. *Howard R. Bierman, M.D., Earl R. Miller, M.D., Ralph L. Byron, Jr., M.D. and Kenneth S. Dod, M.D., San Francisco, Calif.* (From the Laboratory of Experimental Oncology, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, and the Division of Radiology and Cancer Research Institute, School of Medicine, University of California Medical Center.)

Cardiac catheters have been inserted into the carotid arteries and the following branches of the aorta have been entered: celiac axis, superior mesenteric, inferior mesenteric, renal, lumbar, middle sacral and iliac arteries, as demonstrated with radio-opaque media. The arterial patterns of the liver, kidney and areas supplied by the various vessels have been demonstrated. Hepatic metastases have been detected by peculiar vascular patterns.

The supracardiac vessels have been catheterized via the femoral arteries when cervical masses prevented exposure of the carotids.

This technic has enabled a more direct attack on visceral neoplastic tissue both therapeutic and investigative. Wound infection involving the artery, marked arteriosclerosis, large cervical masses and the usual dangers of cerebral

arteriography are the hazards and contraindications of this procedure.

STUDIES ON HUMAN BRAIN SLICES RESPIRATION. *H. W. Elliott, M.D. and V. C. Sutherland, M.D., San Francisco, Calif.* (From the Division of Pharmacology and Experimental Therapeutics, University of California Medical School.)

Through the cooperation of the Division of Neurological Surgery and the Langley Porter Clinic, samples of cerebral cortex were obtained from patients undergoing prefrontal lobotomy operations. The tissue was immediately chilled and slices prepared with a razor and template for study by the direct method of Warburg.

This tissue behaved more consistently and respired at a higher rate than cortex obtained from patients undergoing operations for the removal of brain tumors. In glucose-Ringer's the 30 minute Q^{O_2} was 1.5, falling to 1.2 at 180 minutes. Approximately the same values were obtained when the substrate was pyruvate, lactate or succinate. Glycogen failed to raise the Q^{O_2} above the endogenous level. It is of interest that the Q^{O_2} in the presence of succinate was not elevated above the value in glucose-Ringer's as is the case for rat brain.

The endogenous 30 minute Q^{O_2} was 1.4, falling to 0.6 at 180 minutes. The decline is more gradual than that of rat brain and is apparently not a dilution effect, since it was not appreciably influenced by a tenfold variation in the amount of tissue placed in the Warburg flasks. The endogenous respiration is not inhibited by 0.002 M sodium azide which strongly inhibits glucose oxidation presumably through the formation of a cytochrome-azide complex. This suggests that reactions resulting in oxygen consumption in the absence of substrate (endogenous respiration) are not proceeding through the main line of biologic oxidation.

Differences are also apparent in the action of the drugs tested to date. Methadone (0.001M) stimulates the oxidation of glucose but inhibits endogenous respiration. Sodium pentobarbital (0.002M) inhibits the oxidation of glucose more than it inhibits the endogenous respiration. Morphine (0.002M) has no effect on either.

On five human subjects, control Q^{O_2} values obtained *in vivo* by a modified Kety-Schmidt nitrous oxide method were compared with *in vitro* $Q^{O_{2.8}}$ obtained on samples of their frontal lobe cerebral cortex. The 30 minute Q^{O_2} in glucose-Ringer's averaged 1.53 as compared to 1.68 by *in vivo* measurements.

Case Report

Pharmacologic and Physiologic Studies of a Case of Pheochromocytoma*

ALVIN P. SHAPIRO, M.D., HARRISON M. BAKER, M.D., MURRAY S. HOFFMAN, M.D. *and* EUGENE B. FERRIS, M.D.

Cincinnati, Ohio

THE diagnosis of pheochromocytoma is complicated by the fact that persistent hypertension may be a manifestation of this disease. Moreover, the arteriolar changes associated with benign and malignant hypertension may often be present. The paroxysmal elevations which constitute the typical syndrome of pheochromocytoma and which must be distinguished from similar fluctuations occurring in the natural course of essential hypertension may be entirely absent with tumors of chromaffin tissue.

In both the paroxysmal and chronic forms of hypertension due to pheochromocytoma the definitive diagnosis depends upon the demonstration of large amounts of circulating epinephrine or epinephrine-like substances associated with the hypertension. Beer and his co-workers[1] were able to show the presence of a pressor substance in the blood by bio-assay but this finding has not been consistent. More recent efforts have attempted to show this indirectly, either through the use of supposedly specific epinephrine-producing stimuli or drugs which are epinephrine antagonists.

A case of pheochromocytoma has allowed us the opportunity to compare in a single patient the physiologic and pharmacologic specificity of a number of these diagnostic procedures, including blood pressure responses to histamine, mecholyl, epinephrine, tetraethylammonium chloride, dibenamine® and benzodioxane. In addition the case study has pointed up some of the adaptive mechanisms involved in this disease. Since the original reports concerning the various tests we have employed, additional results have accumulated as isolated case reports in the literature. This material has been reviewed and is presented before proceeding to the presentation of the results in our case and to an evaluation of the specificity of the various tests.

Benzodioxane (933F). Although the adrenolytic property of the benzodioxane compounds has been known since 1933 when Fourneau and Bovet investigated them extensively,[2] it was not until recently that the compounds were employed to aid in the diagnosis of pheochromocytoma. In 1947 Goldenberg, Snyder and Aranow[3] used one of the benzodioxane compounds (933F) in four cases of pheochromocytoma with fixed hypertension. In these cases the drug produced a prompt fall to normotensive levels which persisted for about fifteen minutes. Tests by Goldenberg et al. on twenty-eight patients with other forms of hypertensive disease revealed absence of this depressor response in all cases. One of us[4] has administered benzodioxane in the doses recommended by Goldenberg et al. to thirty patients with essential hypertension with and without renal disease and obtained similar results. These studies illustrate the rather striking specificity of the drug.

Experimentally, the benzodioxanes have both sympatholytic and adrenolytic effects.

* From the Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati General Hospital, Cincinnati, O. This work was supported in part by a grant from the American Foundation for High Blood Pressure. Presented before the Twenty-second Annual Meeting of the Central Society for Clinical Research, Chicago, Ill., November 4, 1949.

However, smaller dosages of 933F as used in the test have only the adrenolytic property.[5] With increasing dosages of 933F within the adrenolytic range the response to epinephrine is first diminished, then abolished and ultimately reversed; furthermore, it has been demonstrated that the degree of depressor response to benzodioxane is directly proportional to the amount of circulating epinephrine, presumably since the effect is only on epinephrine E.[5–7] There is indication that the response does not involve the nervous system in that pithing does not abolish the action of the drug in rats.[4] Benzodioxane does not abolish the effect of epinephrine on the heart rate or the electrocardiographic responses of the heart to injected adrenalin but it may afford slight protection to the myocardium against the lethal effects of large doses.[8]

Dibenamine Hydrochloride.® Spear and Griswold have reported a case of pheochromocytoma in which dibenamine® was of diagnostic and therapeutic value. This was a case of fluctuating hypertension with severe paroxysms. Administration of this drug lowered the blood pressure to normal levels and eliminated paroxysms for a period of forty-eight hours, during which time the patient had considerable symptomatic improvement.[9]

The mode of action of dibenamine® has not been completely clarified, but the work of Hecht and Anderson[10] and of Goodman and Nickerson[11] has shown it is apparently both sympatholytic and adrenolytic. The drug blocks the rise in arterial blood pressure due to epinephrine and apparently partially blocks the mechanisms controlling resting vascular tone. It does not, however, block the rise in cardiac output, the sinus tachycardia, increased peripheral blood flow or increased respiratory volume seen after injection of epinephrine in man. It has been postulated that the drug acts on the neuro effector cells where it blocks the action of sympathin E and epinephrine E, perhaps through competition for the M substance.

Histamine. The use of an intravenous injection of 0.025 to 0.05 mg. of histamine base to induce an attack by the elaboration of epinephrine was first suggested by Roth and Kvale in 1945.[13] Their original experiment was based on an attempt to determine whether histamine might be used to counteract the rise in blood pressure which often occurs in cases of pheochromocytoma at operation, but they found that instead it caused a marked rise in pressure and precipitated an attack. They originally reported three positive tests in three cases of pheochromocytoma, a positive test being based on the production of a pressor response in which the systolic rise was approximately 100 mm. Hg above that produced by the cold pressor test. A marked rise was not considered significant if the patient was also a hyperreactor to the cold pressor test.

We have been able to find in the literature a total of sixteen cases reported by various investigators in which the histamine test was used in proved cases of pheochromocytoma.[9,13–23] Of these twelve were considered positive while four were negative. The negative tests included three patients[15,18,23] in whom the hypertension was persistent, i.e., above 150/100 mm. Hg consistently, while the fourth negative test[17] was in a patient who was under basal anesthesia at the time of testing. The twelve positive cases include two[13,16] in whom the blood pressure was consistently over 150/100 mm. Hg.

The specific mechanism of elaboration of epinephrine from the tumor tissue in this test has been discussed by Calkins and Howard[22] who state, "Presumably vasodilatation is not the cause since nicotinic acid and calcium gluconate do not produce the attack. Pyribenzamine did not prevent the reaction. Dale has shown that histamine causes epinephrine discharge, as evidenced by hyperglycemia, and a rise in blood pressure after an initial fall, and that this does not occur when the adrenals are removed. The mode of action may be a direct adrenal reflex, e.g. initiated by the rapid fall in blood pressure which precedes the rise."

Regardless of the means of elaboration, however, it seems likely that in the reported

positive cases, especially when the typical symptoms of an attack were also present, epinephrine elaboration was responsible for the pressor response.

Mecholyl. Guarneri and Evans[14] reported a case of pheochromocytoma in which the administration of 25 mg. of mecholyl subcutaneously resulted in an initial fall in blood pressure from a control level of 104/80 mm. Hg followed within two minutes by a rise to 210/140 mm. Hg. They tested twenty-seven controls, twenty of whom were essential hypertensives, and seven normotensives with negative results. Bartels and Kingsley[17] reported a positive test, but the patient was under basal anesthesia at the start of the test and the rise did not occur until fifteen minutes after injection. Mayock and Rose[24] reported a rise from 120/80 mm. Hg to 300/180 mm. Hg occurring within two minutes after subcutaneous injection of 10 mg. of mecholyl. Roth and Kvale,[13] using a 2 mg. dose intravenously, did not obtain a pressor response in their case.

Guarneri and Evans were unable to block the pressor response in their case with either atropine, which blocks the muscarinic effects of mecholyl, or with curare, which they assumed should block the nicotinic action of the drug. They concluded that there was probably some other direct action of mecholyl on the adrenal gland resulting in the elaboration of epinephrine.

Tetraethylammonium Chloride (TEAC). La Due et al.[16] reported a case of pheochromocytoma in which the injection of 100 mg. of TEAC resulted in a marked rise in pressure from 175/105 to 270/160 mm. Hg. Bartels and Kingsley[17] reported a rise of similar magnitude in their case. Roth and Kvale,[15] however, have reported a case in which no such rise occurred.

Slight initial rises in pressure, even when there is an eventual marked fall, are not uncommon when this drug is given intravenously. These rises may well be humoral in origin and in some cases could be due to epinephrine.[25] There is evidence[26,27] that epinephrine potentiation can occur with release of autonomic tone which TEAC accomplishes; hence pressor responses might be quite marked when large amounts of circulating epinephrine are present. There is also the possibility that epinephrine elaboration may occur as a reflex adrenal stimulation following initial blood pressure fall or release of autonomic tone.

Adrenalin Sensitivity. Mayock and Rose[24] demonstrated in a case of pheochromocytoma with paroxysmal hypertension that there was no change in blood pressure after the injection of 1.5 cc. of 1:1,000 adrenalin subcutaneously and that it required 2 cc. to elevate the pressure significantly. After surgical removal of the tumor 0.25 cc. of 1:1,000 adrenalin produced a substantial rise in pressure. Mortell and Whittle[28] reported a case in which no rise in blood pressure was observed after subcutaneous injection of 0.75 cc. of 1:1,000 adrenalin.

Although no control studies were done by either of these investigators, it seems clear that this lack of response represents a diminution of sensitivity to exogenous adrenalin. In almost all instances in which patients have had surgery the need for large amounts of adrenalin postoperatively and the tolerance of the patients to these large doses have been observed. Cameron, in attempting to treat individuals with anxiety states by "desensitization to adrenalin," reported that with daily injections of adrenalin in increasing doses blood pressure and pulse responses decreased as did subjective symptoms of pallor and tremor. In some cases the tolerated doses were increased as much as sixfold with daily injections over a thirty-day period.[29] The mechanism of the development of this tolerance to exogenous adrenalin is not understood although the fact that epinephrine responses appear to be augmented in animals after TEAC suggests that the autonomic nervous system may be involved.[26,27]

CASE REPORT

H. J., a thirty-seven year old Negro woman, was admitted to the hospital on November 22, 1948, with the chief complaints of transient

dizzy spells, weakness, fatigue, profuse sweating and weight loss. She had had paroxysmal nocturnal dyspnea and othopnea for three weeks and ankle edema for one month. Nausea and vomiting, accompanied with generalized abdominal pain more marked in the left upper quadrant, had appeared three days prior to admission. She also stated that for four years she had been having recurrent flushing sensations which started in the epigastrium, moved up substernally and caused palpitation and headaches. These could sometimes be precipitated by the patient lying on her left side or abdomen.

The patient had been seen at Cincinnati General Hospital three times between 1937 and 1944; at these times her blood pressure was normal and she gave no history of cardiovascular symptoms. In 1944 during delivery of her second child a moderate elevation of blood pressure was noted but it promptly returned to normal after delivery. In 1946 while hospitalized for an infected abortion she complained of palpitation, bitemporal headaches, heat intolerance, anxiety and weight loss of 25 pounds. Physical examination revealed no evidence of cardiovascular disease and the blood pressure was normal. The thyroid was palpable and nodular, and a coarse, inconstant tremor of the fingers was present.

In April, 1948, she was hospitalized because of multiple complaints, the most prominent being nose bleeds of two weeks' duration. It was at this time that she was noted to have hypertension which she said had been first detected by a private physician late in 1946, since which time she had suffered moderate exertional dyspnea. Blood pressure during the hospital stay ranged from 150/100 mm. Hg to 190/120 mm. Hg, with the exception of a single reading of 120/90 mm. Hg. Grade III retinopathy and evidence of minimal renal damage were present. Of interest in view of later developments was a fasting blood sugar of 130 mg. per cent with a flat glucose tolerance curve. The patient improved during six weeks of symptomatic treatment and was discharged with the diagnosis of essential hypertension.

The patient was not seen again until readmission in November, 1948, at which time physical examination revealed a blood pressure of 240/150 mm. Hg, pulse of 100 per minute and respiratory rate of 24 per minute. Pulsus alternans was noted. The fundi showed numerous fresh hemorrhages and exudates, marked arteriovenous nicking, arteriolar spasm and papilledema of moderate degree. The right pupil was larger than the left, and there was a horizontal nystagmus more marked on right lateral gaze with quick component to the right. The thyroid was nodular, twice normal in size, with the left lobe predominant. Lungs were clear. The heart was slightly enlarged to percussion, rhythm was regular and an apical systolic gallop was heard. There was tenderness in the left upper quadrant of the abdomen and the liver edge was palpable 8 cm. below the right costal margin. The right kidney and the lower pole of the left kidney were easily palpable but considered to be of normal size. Palpation in both flanks and change in position failed to elicit any significant rise in blood pressure. There was minimal pedal edema. Neurologic examination, aside from the eye findings, was normal.

Urine showed a specific gravity of 1.011, with 2+ albumin, no sediment and a negative culture. Hemoglobin, red and white cell count and differential count were normal. Blood urea nitrogen was 20 mg. per cent, fasting blood sugar 130 mg. per cent, carbon dioxide combining power 44 volumes per cent, and chlorides 557 mg. per cent. Chest x-ray, flat films of the abdomen and intravenous pyelograms were normal. Electrocardiogram showed only a prolongation of the Q-T interval (0.34 with a rate of 120). The initial cerebrospinal fluid pressure was 240 mm. H_2O. Dynamics were normal. Cerebrospinal fluid protein was 25 mg. per cent.

The glucose tolerance test with the oral administration of 100 gm. of glucose revealed a mildly diabetic curve:

Time (min.)	Fasting	30	60	120	180
Blood sugar (mg. per cent)	130	153	190	208	105

The insulin tolerance test with the intravenous administration of 0.1 unit of regular insulin per kg. of body weight showed a slight delay in return to pretest levels:

Time (min.)	Fasting	15	30	45	60	90	120
Blood sugar (mg. per cent)	131	106	76	71	64	86	101

Urinary 17-ketosteroids were 1 mg. in twenty-four hours (normal 5 to 10 mg.). Proteolytic

enzymes of blood plasma (plasmin) were greatly increased.*

The patient was digitalized, placed on a low salt diet and given mercurial diuretics as needed to stabilize her weight. During the course of the next ten days the tests outlined and discussed hereafter were performed. On the basis of these tests a diagnosis of pheochromocytoma was made and operation was performed on January 15, 1949. During the preoperative period the blood pressure ranged from 215/130 mm. Hg to 240/155 mm. Hg, with no sudden changes. The patient was asymptomatic and cheerful except for occasional complaints of tremulousness and flushing. Physical examination showed no change other than disappearance of the edema and the enlarged liver.

Anesthesia was inducted with pentothal and maintained with gas-oxygen-ether mixture. The adrenals were exposed through a transverse abdominal incision. The blood pressure did not change with this procedure. A tumor weighing 53 gm. was found arising from the left adrenal gland and extending medially behind the pancreas. The blood pressure dropped step-like with the tying off of each small blood vessel to the tumor from a preoperative level of 220/130 to 170/120 mm. Hg. Whole blood, 500 cc., was given during the course of the operation. When the tumor was finally removed, the blood pressure dropped precipitously to 60/? mm. Hg and respirations ceased. Pressure breathing and adrenalin intravenously immediately restored the pulse and respirations. For a short period the blood pressure made wide swings from shock levels to hypertensive levels as the adrenalin dosage was regulated, but at no time was it below 90/60 mm. Hg for more than one minute.

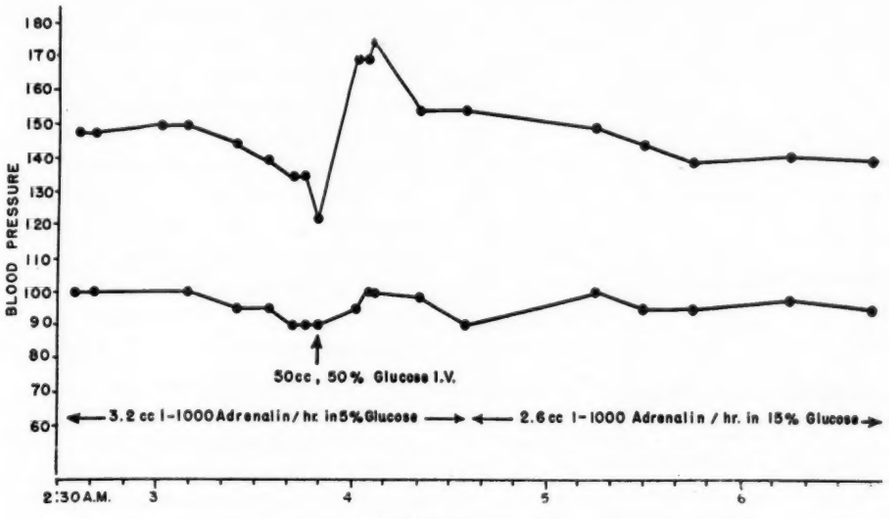

FIG. 1. Response of blood pressure to intravenous glucose. Administration of 50 per cent glucose, while adrenalin infusion was at a constant rate, produced a marked pressor response. Increasing the glucose concentration of adrenalin infusion from 5 to 15 per cent resulted in a reduction of the amount of adrenalin required to maintain the blood pressure at a constant level.

The patient was returned to the ward where a constant intravenous infusion of adrenalin finally stabilized the blood pressure at levels ranging from 100–160/80–110 mm. Hg. Approximately 7 cc. of 1:1,000 adrenalin (7 mg.) per hour in 5 per cent glucose were required, and slight changes in the rate of infusion influenced the level of the blood pressure considerably. Adrenal cortical extract, 20 cc., was added to the infusion and the patient was placed on nasal oxygen. During the next forty-eight hours the patient's adrenalin requirement gradually dropped to 1.3 cc. per hour. However, she developed a stiff neck, areflexia and a Babinski sign on the right. The pupils were widely dilated and did not react to light. Fundi showed marked arterial spasm. Lumbar puncture revealed normal dynamics and normal cerebrospinal fluid. Since 50 per cent glucose diminished the adrenalin requirement and made the patient more alert, it was given several times during this

* Assay performed at the May Institute for Medical Research.

period. In addition the glucose concentration of the infusion was increased. The effect of this increase on blood pressure and adrenalin requirement is illustrated in Figure 1. Normal saline by hypodermoclysis and penicillin were administered and 10 cc. of adrenal cortical extract

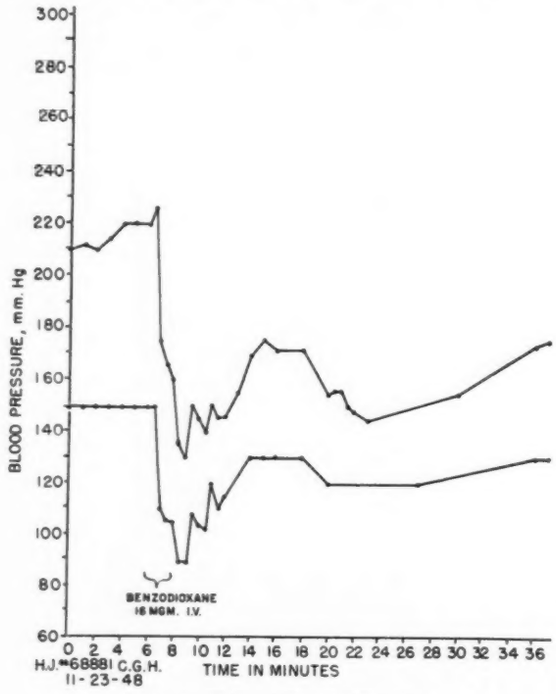

FIG. 2. Effect of benzodioxane.

were added to each 500 cc. of infusion. Adrenalin in oil, 4 cc. of 1:500, and intravenous benzedrine, 2 mg., failed to diminish the intravenous adrenalin requirement. By the fiftieth hour the patient became anuric. The adrenalin requirement began to increase and eventually the gradually falling blood pressure failed to respond to undiluted 1:1,000 adrenalin. The patient died sixty-three hours after operation. Total adrenalin given was approximately 200 mg.; total adrenal cortical extract given was 80 cc.

The striking finding at autopsy was marked pallor of all the viscera. The significant microscopic findings were as follows:

The right adrenal appeared normal although there was abundant cortical vacuolization and the zona fasciculata appeared somewhat shorter than usual. The lungs showed a moderate amount of congestion. The heart revealed marked atherosclerosis, myocardial hypertrophy and moderate edema although no acute degenerative changes were seen. There was severe central necrosis of the liver. The kidney showed changes characteristic of those seen in benign nephrosclerosis, and the glomeruli were all viable. In addition a widespread acute necrosis was superimposed in the tubular system, particularly in the distal convoluted segments, presenting a picture resembling that of a "shock kidney" with lower nephron nephrosis. Microscopic sections of the brain were non-contributory.

The tumor removed at operation measured 5 by 5 by 3 cm. Its surface was smooth and its background color was purplish grey with mottled areas of bright orange. Section revealed an ovoid cystic cavity 3 by 4 by $2\frac{1}{2}$ cm. containing gross blood. The wall of this cavity comprised the principal solid part of the tumor. The tissue was greyish white, slightly gelatinous in nature and presented many areas of gross hemorrhage, some of which had formed small cysts ranging from 1 to 3 mm. in diameter. The grayish tissue was surrounded by a thin rind of bright orange tissue, presumably cortex.

Microscopically, sections of the tumor stained with hemotoxylin-eosin were composed largely of epithelial cells, many of which showed marked variation in size and outline. In many areas these were arranged to form a syncytium separated by interlacing bands of connective tissue. Some of the cells were multinuclear, with the nuclei varying markedly in size and configuration. No mitotic figures were seen. The cytoplasm stained slightly basophilic, contained numerous vacuoles and presented a finely granular appearance. Some cells contained a granular, dark brown material within the cytoplasm. There were areas of recent focal hemorrhage and extravasation of blood as well as heavy deposits of hemosiderin.

With cresyl violet stain a few of the cells were seen to have nuclei with nucleoli and linin networks resembling primitive neural ganglion cells. In the cytoplasm of some of these cells a granular blue staining material resembling Nissl substance was present. Occasional cells showed processes resembling neurons.

Bodian's silver stains did not demonstrate the presence of neurofibrils. However, the tissue had been fixed in Zenker's solution which lessens the effectiveness of this technic. The similarity between the nuclei in some of the tumor cells and those in primitive ganglion cells was clearly demonstrated with Mallory's phosphotungstic acid stain although no glia cells were observed.

The pathologic diagnosis was pheochromocytoma, mixed type, with pheochromocyte cells predominating.

Bio-assay of the tumor extract, prepared according to the method of Bertrand[30] and tested on the pithed rat preparation of Shipley and Tilden,[31] revealed a total of 30 mg. of adrenalin in 53 gm. of tumor tissue. Since two days elapsed between the preparation of the extract and the testing and since several days following the test the extract showed no pressor activity, it was believed that the actual adrenalin content of the tumor had been greater. The pressor response elicited by the tumor extract in the rat was abolished by benzodioxane.

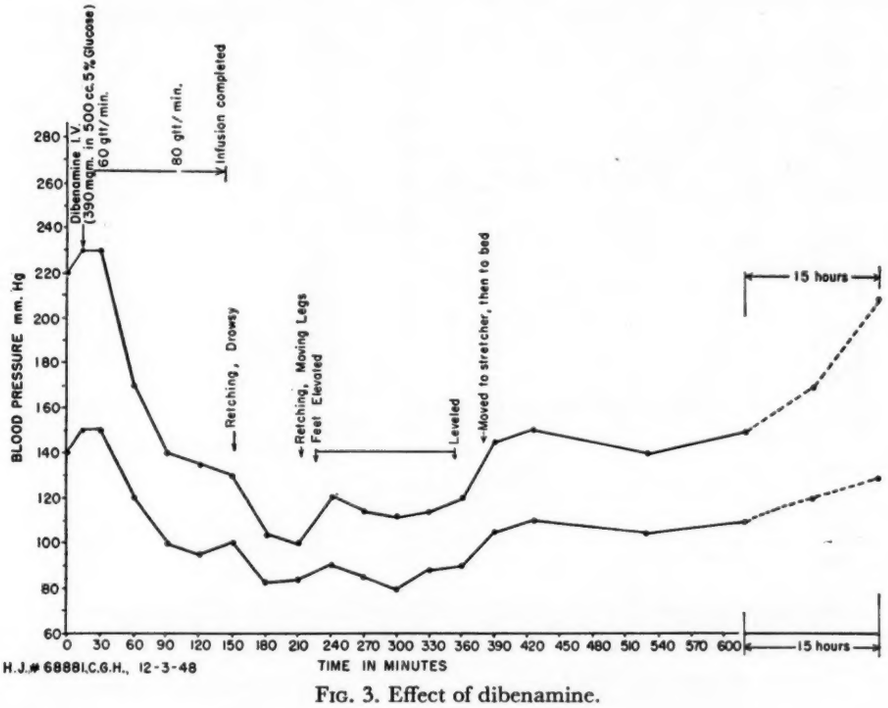

FIG. 3. Effect of dibenamine.

SPECIAL STUDIES

The following diagnostic tests were all performed with the patient in a supine position; blood pressures were taken with a mercury manometer at the time intervals indicated on the figures. Control readings were taken at minute intervals until stabilization occurred prior to each injection.

*Benzodioxane (933F).** Benzodioxane, 16 mg., was given intravenously. Dosage and injection rate were those recommended by Goldenberg et al.[3] From a control level of 210/150 mm. Hg, blood pressure began to fall during the first thirty seconds of injection reaching its lowest level, 130/90 mm. Hg, within one minute after completion of injection. It gradually rose thereafter, reaching the control level in one hour. (Fig. 2.)

*Dibenamine Hydrochloride.** Dibenamine hydrochloride,® 390 mg. (7 mg. per kg. body weight), was given by intravenous drip in 500 cc. of 5 per cent glucose, the infusion requiring approximately two and a half hours for completion. From a control level of 230/150 mm. Hg the blood pressure reached its lowest level, 100/80 mm. Hg, one hour after completion of the infusion. At this level the patient although drowsy showed no evidence of shock and the blood pressure could be elevated 10 to 20 mm. Hg by active or passive movement of the extremities. It remained below control levels for approximately twenty-four hours. (Fig. 3.) Slight postural hypotension persisted for at least another twelve hours. The patient experienced considerable relief from the symptoms of headache and nervousness,

* Benzodioxane supplied by Merck & Co., Inc.

* Dibenamine hydrochloride® supplied by Smith, Kline, & French Laboratories.

which outlasted the depressor effect on the blood pressure.

*Tetraethylammonium Chloride (TEAC).** During the previous hospital admission in April, 1948, administration of 4 cc. (400 mg.) of TEAC resulted in an immediate marked rise in blood pressure which reached its height within one minute and remained above control levels for at least thirty minutes. (Fig. 4.) On the present admission 1 cc. (100 mg.) of TEAC was given through a three-way stopcock attached to an intravenous infusion of normal saline. From a control level of 235/150 mm. Hg the blood pressure began to rise immediately, reaching systolic levels beyond the range of the manometer (300 mm. Hg) within two and a half minutes. Benzodioxane, 20 mg., was then given intravenously. The blood pressure fell immediately, reaching 145/100 mm. Hg within one and a half minutes after injection and remained below control levels for at least one hour. Marked symptomatic relief followed the injection of benzodioxane. (Fig. 4.)

* Etamon chloride supplied by Parke, Davis & Co.

Histamine and Mecholyl. Histamine base administered according to the method of Roth and Kvale[13] and mecholyl given as advised by Guarneri and Evans[14] caused a fall in blood pressure. (Fig. 5.) The rise

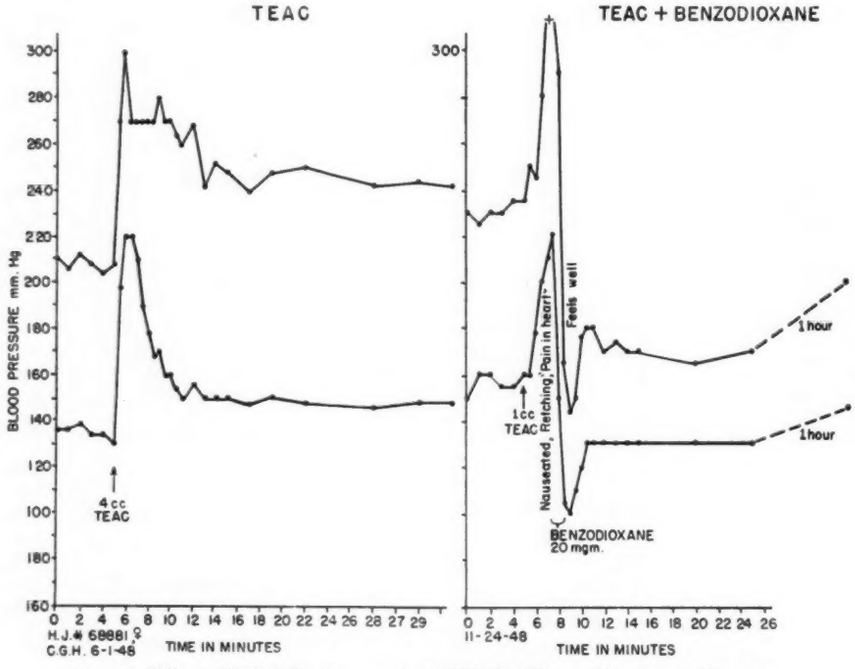

FIG. 4. Effect of TEAC alone and of TEAC followed by benzodioxane.

TABLE I
RESPONSES OF NORMALS AND HYPERTENSIVES TO INTRAVENOUS ADRENALIN

	Initial Blood Pressure	Amount of Rise	Dose (1–10,000) (cc.)	Time of Maximum Rise (min.)
Normals	115/80	60/30	0.5	1
	110/80	40/5	0.5	1
	130/65	50/0	0.5	1
	108/68	67/7	0.5	1
	110/70	40/15	0.5	1
	105/65	35/5	0.25	1
	110/60	42/14	0.25	1
Hypertensives	195/105	35/10	0.25	1
	160/110	50/10	0.25	1
	170/110	30/0	0.25	1
	218/114	56/6	0.25	1
	215/145	70/10	0.25	1
	240/160	28/10	0.25	1½
		40/0	0.5	1½
	200/95	50/11	0.25	1½
	150/95	100/20	1.0	2

reported to be characteristic of pheochromocytoma was not observed.

Adrenalin Sensitivity. Adrenalin, 1:10,000, was given through a three-way stopcock attached to an intravenous infusion of normal saline. Doses of 0.25, 0.50, 1.0 and 1.5 cc. were administered. Between injections the blood pressure was permitted to stabilize and an additional ten-minute interval was allowed before the next injection. As can be seen in Figure 6 it was not until 1.0 cc. had been administered that any significant pressor response occurred, and 1.5 cc. caused no greater effect. Subjective symptoms due to adrenalin were minimal.

To compare with the aforementioned response a series of seven normotensive and eight hypertensive patients have been tested with adrenalin in a similar manner. The results are compiled in Table 1. In all cases 0.25 and 0.50 cc. doses, which caused no response in the case of pheochromocytoma, produced a significant rise in systolic

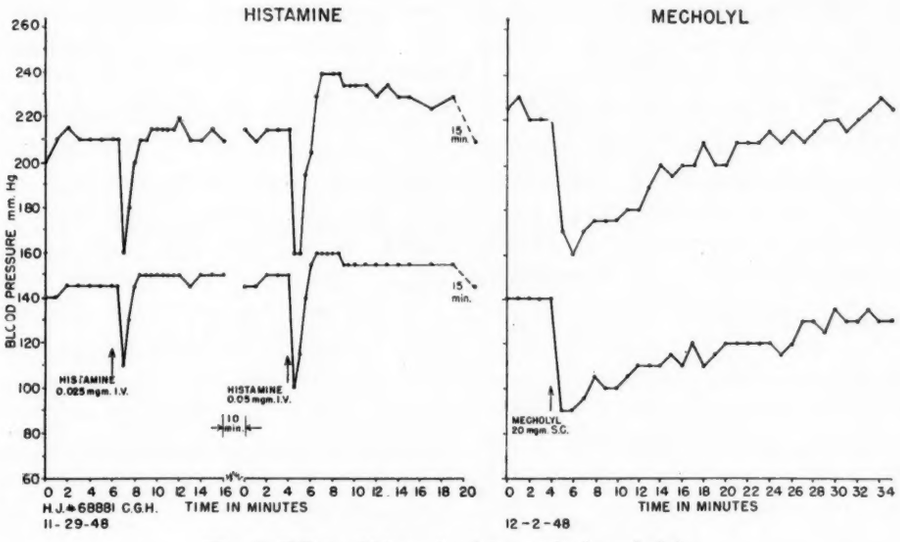

FIG. 5. Effect of histamine base and of mecholyl.

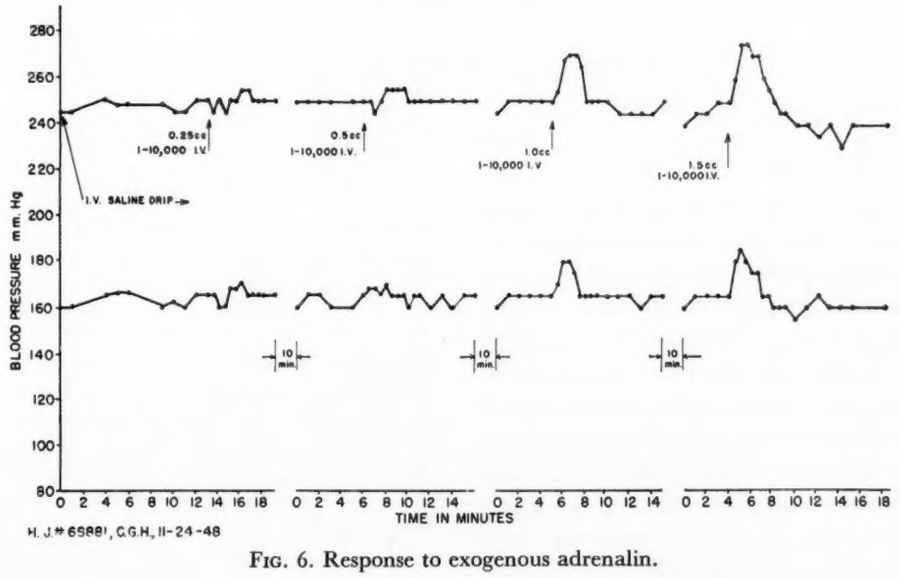

FIG. 6. Response to exogenous adrenalin.

pressure. Diastolic pressure was relatively unaffected.

The results of these various diagnostic tests are summarized in Table II.

TABLE II
SUMMARY OF TESTS

Test	Date	Route of Administration	Dose	Control Level of Blood Pressure	End Point (Blood Pressure at Height of Effect)	Time of End Point
Benzodioxane	11/23/48	I.V.	16 mg.	220/150	130/90	3 min.
Dibenamine®	12/3/48	I.V.	390 mg.	230/150	100/75	3½ hr.
TEAC	6/1/48	I.V.	400 mg.	210/130	300+/220	2 min.
					250/150	10 min.
TEAC and benzodioxane	11/24/48	....	.....	.....	.....	.....
a) TEAC		I.V.	100 mg.	235/150	300+/220	2 min.
b) Benzodioxane		I.V.	20 mg.	300+/220	145/100	1½ min.
Adrenalin 1–10,000	11/24/48	I.V.	0.25 cc.	250/165	250/168	2 min.
			0.50 cc.	250/165	255/170	2 min.
			1.0 cc.	250/165	270/180	2 min.
			1.5 cc.	250/165	275/180	2 min.
Histamine	11/29/48	I.V.	0.025 mg.	210/145	160/110	1 min.
					215/150	5 min.
			0.05 mg.	215/150	160/100	1 min.
					235/155	5 min.
Mecholyl	12/2/48	S.C.	20 mg.	225/140	160/90	2 min.
					215/120	20 min.

COMMENTS

Diagnostic Problem

The definitive diagnosis of pheochromocytoma rests upon the demonstration of circulating epinephrine as the cause of the hypertension. There are many facts still to be investigated concerning the altered physiology associated with the tumor and the pathways by which the accompanying metabolic disturbances are produced. It is not clear whether epinephrine is continuously or intermittently excreted by the tumor, especially in those patients with paroxysmal hypertension. The mechanism of development of sustained hypertension with and without superimposed paroxysms likewise is still to be clarified.

However, it seems well substantiated that circulating epinephrine or an epinephrine-like substance is the causative factor of the hypertension. Thus when epinephrine in large amounts can be shown to be present in the blood in association with hypertension, an extensive search for the chromaffin tumor is warranted and the expectation that its removal will abate the hypertension is justified.

Many stimuli, ranging from mechanical pressure on the adrenal gland to situations having specific emotional meaning to the patient, will produce an increase in the amount of circulating epinephrine in pheochromocytoma. If a drug is a specific physiologic stimulant to the production of epinephrine, it should call forth the excretion of large amounts of this substance when a pheochromocytoma is present. However, since there is ample evidence that nonspecific stimuli will cause epinephrine elaboration, the mere fact that epinephrine is produced in response to any given drug cannot be taken as proof that the drug is the direct cause in the sense of having direct action on the pheochrome tissue. Furthermore, since many individuals such as those with anxiety states, labile essential hyper-

tension, hyperthyroidism and migraine can have symptoms which mimic those of epinephrinemia, even the appearance of a paroxysm of hypertension, either spontaneously or in response to a given drug, cannot be considered as due to circulating epinephrine unless the paroxysm can be abolished or prevented by a substance which specifically blocks the action of epinephrine.

In our case the lack of the characteristic rise to either histamine or mecholyl may be explained by the considerations concerning specificity which have been mentioned or by the assumption that the tumor was incapable of further increasing its epinephrine production. It is perhaps significant in this regard that four of five of the negative tests reported with histamine have been in patients with persistent hypertension whereas only two of the twelve positive tests were in persistent hypertensives. The specificity of this test may be further questioned, however, in view of the fact that not all of the cases reported as positive might be considered so by the original authors. In some comparison is not made with the reactivity to the cold pressor test, and in one[22] the systolic rise reported is only 60 mm. Hg. In two[14,21] a larger amount of histamine base was used than that suggested by Roth and Kvale.

The specificity of both the histamine and the mecholyl test in diagnosis depends on the proof that in the individual case the pressor response elicited is due to epinephrine. The negative results indicate that the drugs are not specific stimulants to the chromaffin tissue since pheochromocytoma can be present when these tests are negative and that it is desirable to evaluate the pressor responses, when they do occur, by the administration of a specific adrenolytic substance.

Our results with TEAC alone and TEAC followed with benzodioxane indicate the value of the latter drug in identifying the adrenergic nature of a pressor response. The blood pressure rise obtained with TEAC would appear to be humoral in origin since it occurred in the presence of a blockade of the autonomic ganglia. Abolition of this response by benzodioxane indicates that it was adrenergic. The pressor response to TEAC alone cannot be regarded as indicating specifically that epinephrine has either been elaborated or potentiated on the basis of our knowledge of its physiologic action. In addition a pressor response to the drug is occasionally observed in essential hypertension and more frequently in toxemia of pregnancy and acute glomerulonephritis.[25,32]

In cases of pheochromocytoma with persistent hypertension a depressor response produced by a specific adrenolytic substance is the important diagnostic feature. In those cases in which the hypertension is not fixed production of a paroxysm which can be abolished by an adrenolytic agent establishes the diagnosis regardless of the method employed to elicit the paroxysm. Our experience with the effects of TEAC and benzodioxane and that of Spear and Griswold,[9] who were able to eliminate a positive histamine test with dibenamine® in their case, illustrate the value of this approach.

The results in our case indicate the specificity of benzodioxane and dibenamine® in counteracting the pressor activity of circulating epinephrine. Response to benzodioxane seems more specific, however, since no depressor effects* have been encountered in control hypertensives either in our series of thirty cases[4] or in those reported by Goldenberg et al.[3] Including their later unpublished studies they have as yet seen no false positive cases nor have they encountered any false negative cases, i.e., patients who show no depressor response and yet have a pheochromocytoma.[33] The effect of the drug on patients with paroxysmal hypertension during a normo-

* Recently two cases of persistent hypertension have been encountered in which a transient fall in blood pressure, lasting two to three minutes, occurred. In the first case repetition of the test showed negative results, and autopsy did not reveal evidence of pheochrome tissue. In the second case further investigation, as outlined in this paper, did not support the diagnosis of pheochromocytoma.

tensive phase has not been determined; it is probable that in such cases no effect on the blood pressure would be elicited.

Grimson et al. have reported negative benzodioxane tests on sixty-one patients with hypertension and one positive test on the one patient in their series who had a proved pheochromocytoma.[23] Taliaferro, Adams and Haag have reported a presumably false positive test.[34] However, the negative histamine and TEAC tests which they observed do not establish the absence of a chromaffin tumor, nor was an autopsy obtained. In the event that their patient had a pheochromocytoma the apparent development of tolerance to the effect of benzodioxane might be explained by the evidence that hypertension can persist in these patients when the amount of circulating epinephrine has diminished to a level which cannot be detected by benzodioxane.[3]

Dibenamine,® presumably because it has sympatholytic as well as adrenolytic effects in the dosage used, will also lower the blood pressure in some patients with essential hypertension.[12] Haimovici and Medinets have demonstrated these sympatholytic properties in humans.[12] They studied twenty hypertensive patients who received dibenamine,® and were able to show a reduction to normotensive levels in seven of them. Six of these seven patients had benign and one had malignant hypertension. Of the fourteen who had no significant response six had malignant hypertension and seven had "systolic" hypertension. The nature of the response in those patients whose blood pressure fell was indistinguishable from that observed in our case of pheochromocytoma and in that of Spear and Griswold. Therefore, unlike benzodioxane, dibenamine® is not specific in the persistent hypertension of pheochromocytoma. However, it would still seem possible to make use of its adrenolytic effects to eliminate paroxysms as demonstrated by Spear and Griswold.

Our results with the administration of intravenous adrenalin to this patient are in keeping with those of Mayock and Rose[24] and suggest a method of administration which is subject to better control than is subcutaneous injection. There is no evidence in our results as to whether the poor response is due to the development of actual tachyphylaxis to the drug or merely represents a negligible response due to the masking of a small exogenous dose by the larger amount of circulating epinephrine already present. Since adrenalin, like many other stimuli, has been reported to induce paroxysms in pheochromocytoma,[40] the greatest value of the test of adrenalin responsiveness is in patients with persistent hypertension not subject to paroxysms.

Adaptive Mechanisms in Pheochromocytoma

Endocrinologic Disturbances Associated with Pheochromocytoma. There are many reports in the literature concerning disordered function of other endocrine systems in pheochromocytoma. Diabetes may exist and disappear after removal of the tumor.[21,36] Although frank diabetes may be absent the presence of an elevated fasting blood sugar or an abnormal glucose tolerance curve as in our case is not uncommon. These findings may be present only during paroxysms or may be constant in a given case.[28,37–39] Autopsy findings in one case showed hyperplasia of the pancreatic islet tissue.[35]

Elevated basal metabolic rates have also been reported and some patients have shown associated hyperthyroidism.[22] Fibrosis of the thyroid has been reported.[39] Hyperthyroidism was suspected in our case on the basis of the symptomatology and the presence of an enlarged thyroid gland four years prior to the establishment of the diagnosis of pheochromocytoma.

The finding of low urinary ketosteroids in our case suggests altered function of the adrenal cortex. Adrenal cortical function is often disturbed in pheochromocytoma, not only because of pressure and replacement but also through stimulation and ultimate exhaustion and atrophy of adrenal cortical tissue as a result of the effect of epinephrine on the anterior pituitary.[41,42]

These facts suggest that in pheochromo-

cytoma one is dealing with a panendocrinologic disorder rather than uncomplicated overactivity of adrenal medullary tissue.

Physiologic and Toxicologic Effects of Epinephrine. The physiologic effects of epinephrine include mobilization of glycogen from the liver, skeletal muscle and myocardium. Cori[43] has shown that the amount of adrenalin necessary to cause a rise in the blood sugar and lactic acid is one-eighth of that necessary to cause an elevation of the blood pressure, and that the blood sugar and lactic acid response to an initial injection of epinephrine is less than the response to the same dose when administered over a one-hour period.

Freeman, Freedman and Miller[44] demonstrated in dogs that continuous administration of epinephrine resulted in an increased hematocrit with diminution of the plasma volume, loss of circulating body fluid and a drop in blood pressure with shock and ultimate death. This pattern could be interrupted by injections of hypertonic glucose or by transfusions of whole blood. Indirect proof that glucose-glycogen metabolism may be of importance is given by the postoperative response of our patient to hypertonic glucose. (Fig. 1.) Not only did the patient become more alert after such injections but also for a time her adrenalin requirement was diminished. Palmer and Castleman reported a case in which the intravenous administration of 10 per cent glucose gave symptomatic relief during paroxysms.[45] Of interest was the finding by Mortel and Whittle of decreased myocardial glycogen in their case.[28]

The secondary effect of epinephrine on the adrenal cortex through its action on the anterior pituitary has been mentioned. If of sufficient degree to result in cortical depression and some insufficiency, this may contribute to the low blood pressure which frequently follows removal of a medullary tumor. In the light of Selye's theory in which the adrenal cortex figures so prominently in adaptation to stress[46] it is apparent that even mild depression of adrenal cortical function in a patient with pheochromocytoma may increase the operative risk by hindering the return to homeostasis following removal of the tumor.

Raab has postulated that epinephrine may act to stimulate the thyroid (either directly or via the pituitary) and has shown that thyroxin potentiates the normal and toxic effects of epinephrine. Thus the development of hyperfunction of the thyroid with increase of the toxic effects of epinephrine and thyroxin on the heart is a distinct possibility in pheochromocytoma.[8]

"Epinephrine is capable of causing myocardial anoxia as a specific metabolic effect regardless of hemodynamic conditions and regardless of the volume of coronary flow," according to Raab,[8] and the electrocardiographic changes resulting from epinephrine injection are compatible with anoxia and myocardial strain. Cases of angina have been reported with pheochromocytoma. The adrenolytic drugs used in our study, especially dibenamine,® have been shown to exert a marked "heart protective" action against the toxic effects of epinephrine.[8] In the case reported by Spear and Griswold[9] dibenamine® caused marked symptomatic improvement even after the blood pressure had resumed its pretest level. Grimson et al.[23] made use of benzodioxane to stabilize the blood pressure in their patient during surgery. Along with Raab's experimental work these clinical data suggest the possible value of adrenolytic agents in preoperative management, particularly in those individuals with myocardial damage or congestive failure.

Epinephrine has been demonstrated to cause activation of the proteolytic enzyme system (plasmin) of human subjects,[47] and plasmin determinations revealed a very high activity in our patient.

Clinical observations have suggested that the substance discharged by chromaffin tumors is not true epinephrine. Indeed, nor-epinephrine has been identified in one case.[48] In the case reported by Mortell and Whittle[28] assay of the pressor substances from a surgically removed tumor

revealed consistently high potency over a forty-eight-hour period, an observation not characteristic of epinephrine. This, however, was not found in our case when attempts to retest the tumor extract after forty-eight hours revealed loss of pressor activity. Lack of consistent demonstration of abnormal glucose metabolism is also not characteristic of true epinephrine effect. Raab has shown that there are probably a number of fractions secreted by the adrenal medulla which has similar but not identical effects on various organs of the body.[49] Whether or not the substance discharged by the tumor is epinephrine, an epinephrine-like compound or a mixture of such substances does not seem of great clinical importance since the majority of actions of the secreted substance closely follow those of epinephrine. However, the possibility that specific adrenolytic test agents may give an atypical response in the presence of a preponderance of nor-epinephrine requires investigation.

The mode of death in this case deserves comment in regard to the physiologic alterations in pheochromocytoma. Although the pathologic findings fail to clarify the cause of death, the clinical picture resembled that seen in shock with adrenal cortical insufficiency. The patient was apparently unable to readjust to the withdrawal of the large amount of epinephrine to which she had previously been accustomed. Two other cases have been reported with a similar pattern of death following eventual loss of response to epinephrine postoperatively.[28,35]

Although the administration of adrenalin in the postoperative period is usually necessary and can be life saving, the previous comments have indicated that excessive and continued use may have a further deleterious effect on the function of the adrenal cortex as well as on carbohydrate metabolism and myocardial function. Attempts to maintain the blood pressure postoperatively with hypertonic glucose, plasma, whole blood and adrenal cortical preparations may diminish the amount of adrenalin required.

SUMMARY AND CONCLUSIONS

A case of pheochromocytoma with persistent hypertension is presented in which the pharmacologic and physiologic specificity of a number of diagnostic procedures were compared.

Benzodioxane (933F) produced an immediate fall in blood pressure to normotensive levels. Dibenamine® produced a similar fall, slower in onset but longer in duration. Tetraethylammonium chloride (TEAC) produced a sharp rise in pressure which was abolished by benzodioxane. Diminished sensitivity to intravenous adrenalin was demonstrated. Histamine and mecholyl each caused an initial fall in blood pressure, with the pressor response reportedly characteristic of pheochromocytoma being absent.

The results bear out the specificity of benzodioxane and dibenamine® in counteracting the pressor activity of circulating epinephrine. Response to benzodioxane is more specific, however, because no depressor effects have been encountered in a series of control hypertensives whereas such reactions do occur with dibenamine.® Diminished sensitivity to exogenous adrenalin would also appear to have specific meaning in that tolerance to the effect of this drug develops when it is present in the circulation in large amounts. The pressor response to TEAC would appear humoral in nature, specifically adrenergic in this instance since it was abolished by benzodioxane. The lack of pressor response to histamine or mecholyl suggests that these tests are not specific for diagnosis.

These results suggest the specificity of benzodioxane in the diagnosis of pheochromocytoma when the blood pressure is elevated persistently, and the desirability of evaluating the specificity of pressor responses to histamine, TEAC and other stimuli with an adrenolytic agent. The specific physiologic mechanism responsible for epinephrine elaboration with these stimuli is relatively unimportant from the diagnostic standpoint when one can thus

demonstrate pharmacologically that a response was due to circulating epinephrine.

The management of a case of pheochromocytoma must be approached with the realization that the metabolic disturbance is widespread. A physiologic adjustment has been made to the presence of epinephrinemia in which endocrine organs other than the adrenal medulla have been involved. Removal of the tumor disturbs the equilibrium and readaptation must take place. Successful return to homeostasis will depend on the degree to which changes are irreversible and on the judicious use of replacement therapy.

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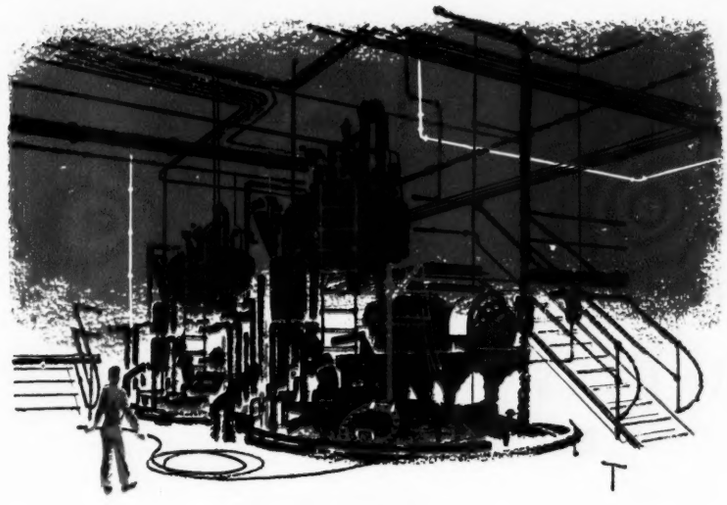

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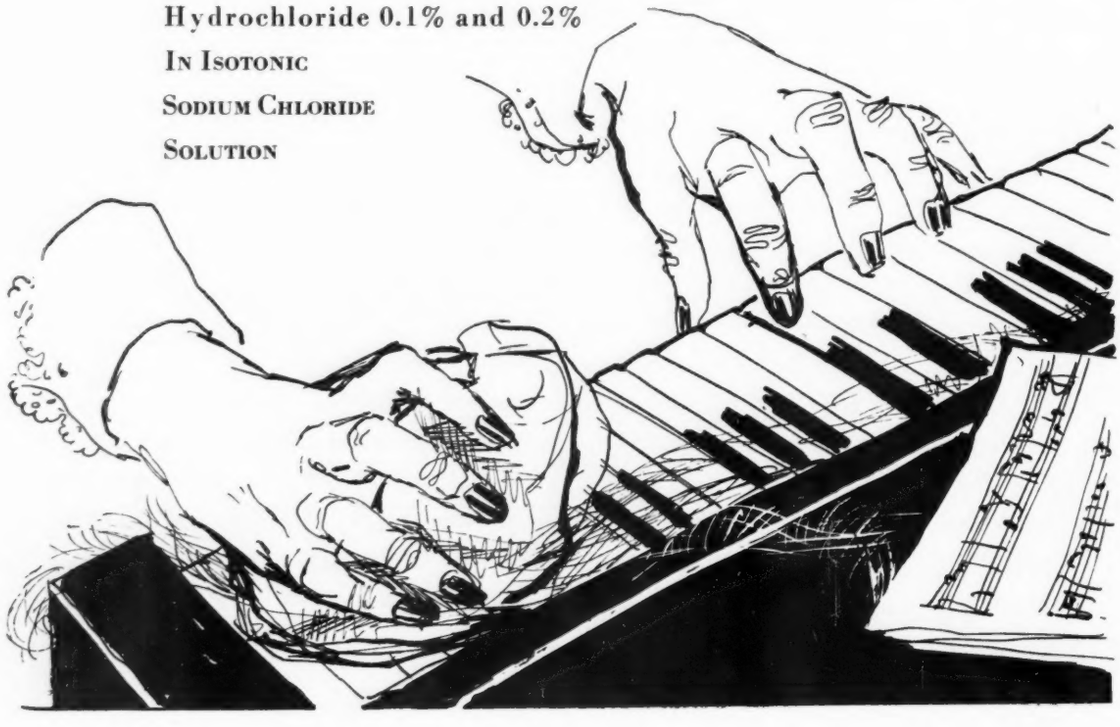

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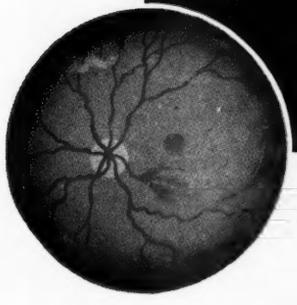

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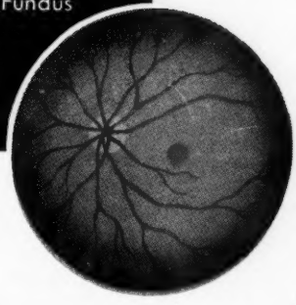

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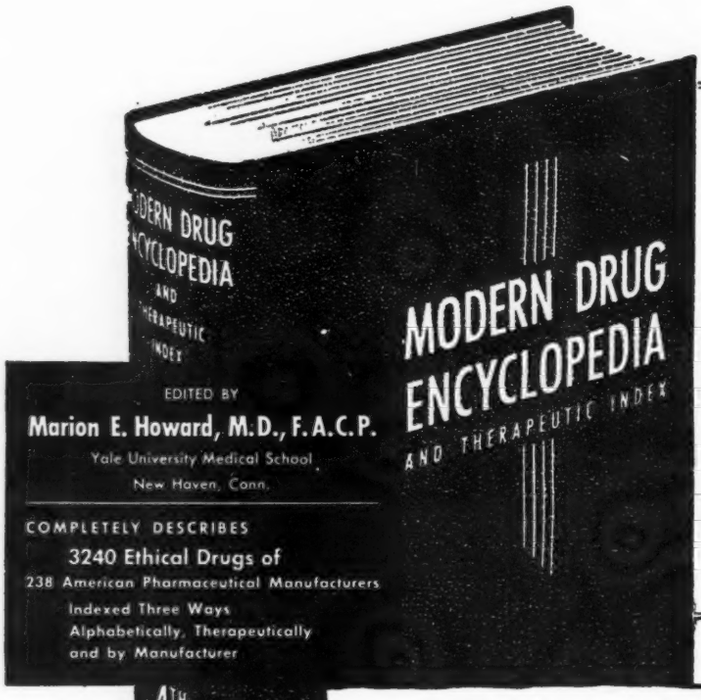

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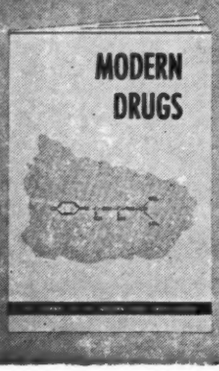

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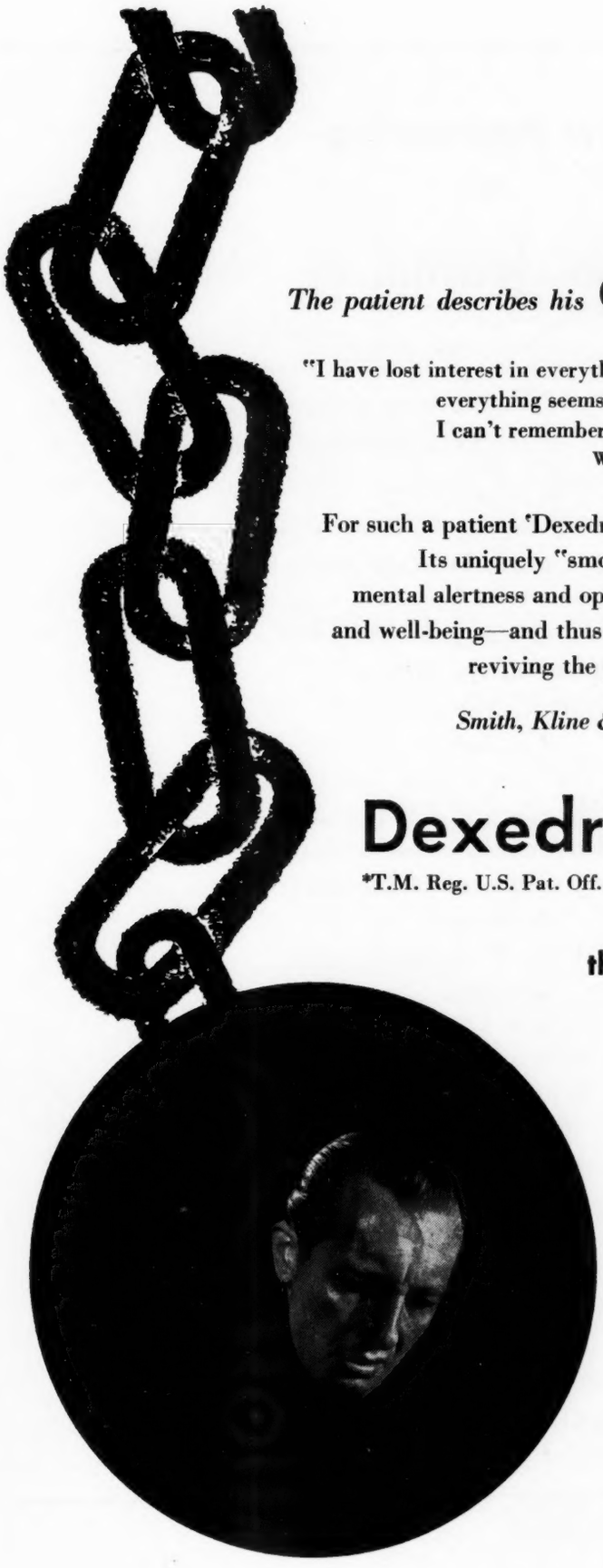

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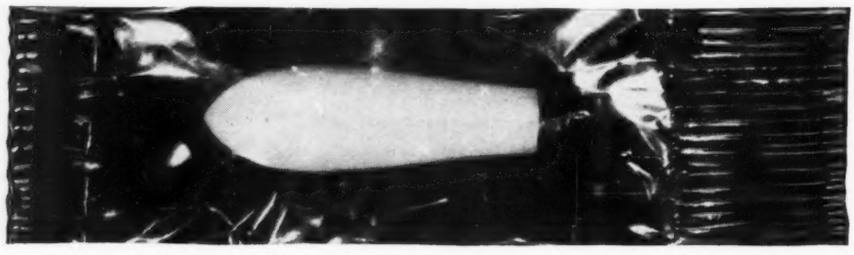

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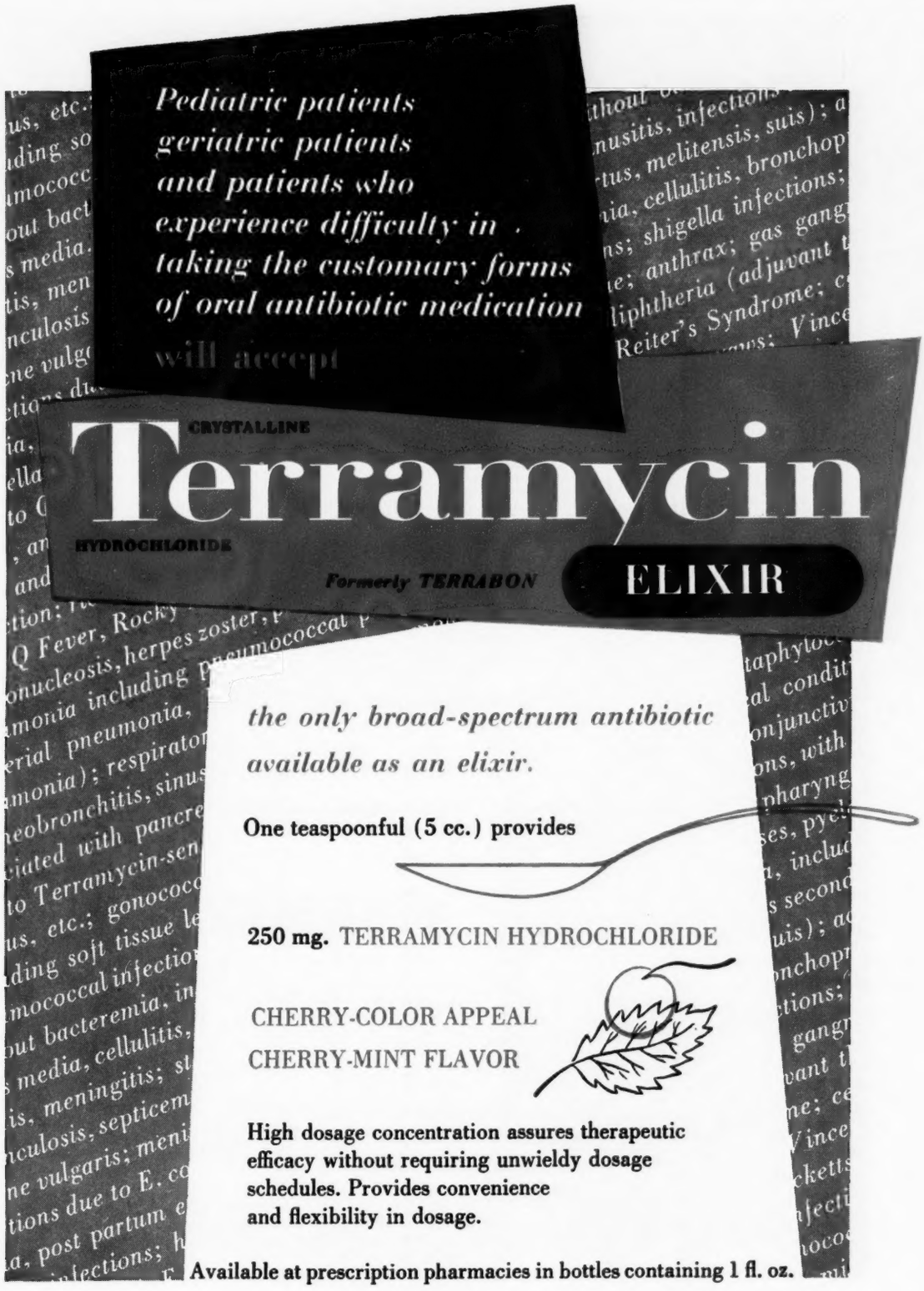

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